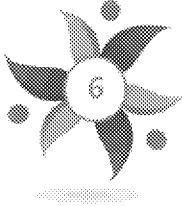


Human Health Risk Assessment (HHRA) Project Planning Tool Project Plan



HHRA Project 6 (*RMS ID# HHRA 3.23*) Cumulative Risk Assessment (CRA) Methods and Applications

Project Leads (PLs): Michael Wright (NCEA CIN) and
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Project start date: 10/01/2015

Project end date: 09/30/2019

Executive Summary

Project 6 in the HHRA portfolio addresses the need to move beyond traditional risk assessment practices by further evolving the state of the science and building capacity to perform CRA. The project pursues further development of analytical methods and case studies to facilitate their application into CRAs. Recent advances in understanding of systems biology, emerging data on epigenetics and genetic polymorphisms, both conceptual and quantitative approaches to characterize the interaction of multiple stressors, and how to best use or interpret multi-media and multi-route cumulative exposure measures such as biomarkers will be explored. Case studies will help address community-based research needs and concerns and further refine approaches by providing important lessons learned. These efforts promote the general goal of the HHRA program under Topic 3 to provide site-specific and regulatory risk assessment support.



Research Project Description

Recent recommendations to address cumulative risk by the National Academy of Sciences (NRC, 2009) have reinforced previous guidance in frameworks to consider mixtures (US EPA, 2002) and multiple stressors (US EPA, 2003). This is in recognition that realistic and relevant environmental exposures of regulatory concern are not only to singular chemicals but also concurrent multiple chemical exposures; and the exposed populations may also have social or genetic factors that may alter their susceptibility to the chemical exposures. Advancing the understanding of the interplay among the various key biological, psychosocial, spatial, and environmental factors, shown in Figure 6-1, and of how these factors contribute to disproportionate risk, will support direct application to place-based characterizations in overburdened communities and help support environmental justice (EJ).

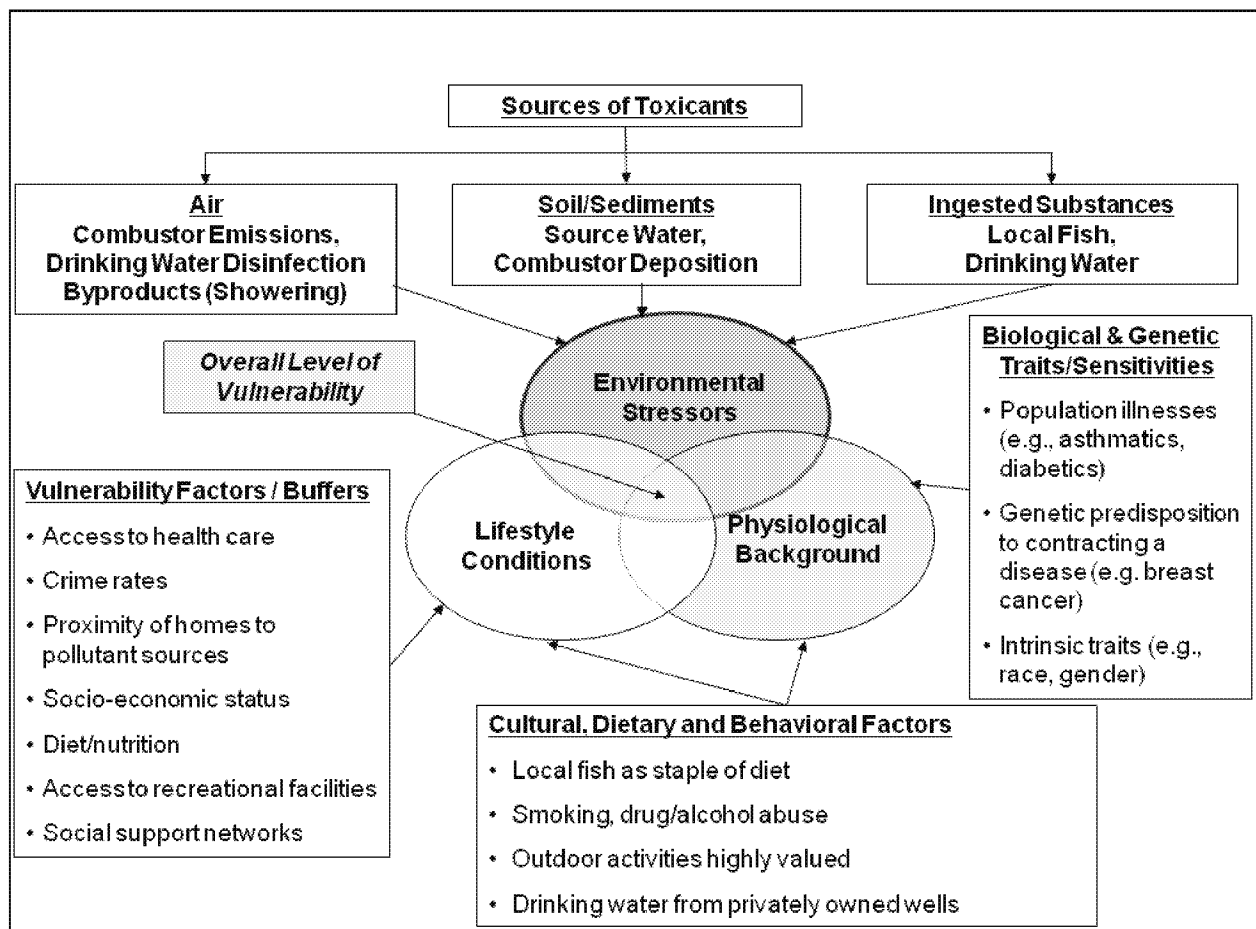


Figure 6-1. CRA framework illustrating potential roles of chemical and non-chemical stressors. Current area of emphasis in HHRA is interaction of ecological and human stressors and active collaboration with the HS and SHC programs to consider resiliency and well-being indices.



CRA is thus viewed as a tool for organizing and analyzing information to examine, characterize, and possibly quantify the combined adverse effects on human health or ecological systems from multiple environmental stressors (Callahan and Sexton, 2007). The need to address this type of problem has been recognized for several decades, but progress has been slow due to insufficient knowledge, inadequate understanding, technologic limitations, and scarce funding (Callan and Sexton, 2007). Advances in biotechnology, for example, analytical capabilities to readily measure biomarkers in various media, computational models to characterize exposures at various scales, and biologically based dosimetry models to describe key events of pathogenesis leading to different disease states, hold promise to improve CRA. This shift to consider cumulative impacts by receptor-oriented CRA approaches is important as it has resulted in various conceptual models to encourage improvements in characterization of the impact of multiple factors, especially because there is no empirically verified theory guiding how best to combine and then assess risks from both chemical and nonchemical stressors (Linder and Sexton, 2011). The NRC (2009) proposed a version of the stressor-based paradigm, modified from Menzie et al. (2007), that discriminates among risk-management options, which can be applied to constructing place-based approaches to address community concerns.

This project builds on the considerable experience and previous publications of HHRA scientists to advance CRA methods and applications (US EPA 2000; 2003; 2007). The proposed tasks incorporate recent advances in understanding of systems biology such as adverse outcome pathway (AOP) and molecular target sequence similarity developed in the CSS program to help support inclusion of ecological indices such as the general ecological assessment endpoints (US EPA 2004). Multi-criteria decision analysis (MCDA) and other computational models will be explored to inform quantitative data integration. Another task will describe elements and considerations for risk characterization and approaches for integrating multiple stressors. Directed acyclic graphs (DAGs), in collaboration with the Environmental Public Health Division of NHEERL, will be evaluated for potential utility in planning, scoping, analysis and characterization of CRA applications. Case studies and a framework for incorporation of epigenetic or genetic data will be developed to inform data integration to define susceptible populations. Exposure and risk apportionment will advance approaches that address community concerns and support risk mitigation strategies.

Project Impact

Research and work supporting CRA is central to advancing the EPA Risk Assessment Forum's CRA Guidelines, and will position the HHRA program to better address place-based assessment activities and thereby support sustainability, climate change efforts, and Environmental Justice (EJ) roadmap goals.

Project Scope

Approaches will be developed to integrate and evaluate impacts of chemical and non-chemical stressors on the environment and health using multi-criteria decision analysis (MCDA) and



computational models to assist quantification and visualization of valuation and missing data. Ongoing EPA CRA activities, including strategic coordination and scientific support to the EPA's Risk Assessment Forum Technical Panel on CRA ([[HYPERLINK "http://www.epa.gov/raf/"](http://www.epa.gov/raf/)]) and providing training on CRA methods, will continue to provide advancements in CRA methods and training. HHRA tasks in this project will further advance methods to incorporate multiple stressors and case studies to test CRA applications, including support in response to specific requests from regions and communities. Lessons learned from previous CRA efforts will advance understanding and serve as the basis for further development of more advanced CRA approaches. Additional research will try to broaden the scope of CRA by developing approaches to evaluate and incorporate epigenetic and genetic polymorphism information to better characterize susceptibility in response to environmental chemical exposures. Evaluation of exposure modeling and guidance on how to apportion exposure and risk from chemical and non-chemical stressors in both human and ecological receptors across various media is another key task anticipated to help advance CRA development. Future work with the HS and SHC programs is expected to consider how to integrate resiliency and well-being indices under development in those programs into the CRA framework.

Project Structure and Rationale

The project is structured into four tasks. Each task area was selected to address important issues in community and cumulative risk assessment (e.g., how to incorporate multiple stressors) or the application of data types that may provide valuable information to advance CRA methods (e.g., epigenetics). The task products, integrated together, comprise a targeted strategy for advancing and applying CRA methods.

- **Task 6.1. (RMS ID# HHRA 3.231) Approaches to Cross-species Data Integration to Support CRA**
- **Task 6.2. (RMS ID# HHRA 3.232) Incorporating Multiple Stressors**
- **Task 6.3. (RMS ID# HHRA 3.233) Applying Genetic and Epigenetic Data to Inform Susceptibility**
- **Task 6.4. (RMS ID# HHRA 3.234) Apportioning Multimedia Exposure and Risk across Receptors**

Measures of success

The tasks in this project will advance the science of CRA by incorporating new data, approaches and applications to develop place-based assessments that better address community concerns and complex stressor scenarios.

**Stakeholders (outside ORD):**

The need for continued advancement and application of CRA methods has long been recognized by the Agency and external stakeholders alike.

References

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Task 6.1
(RMS ID# HHRA 3.231)
Approaches to Cross-species Data Integration to
Support Cumulative Risk Assessment

Task Lead (TL): Meredith Lassiter (NCEA RTP)

Task Start Date: 10/01/2015

Task End Date: 09/30/2019

Task Description:

Advances in the integration of human and ecological data have provided new possibilities for conducting risk assessments that consider the cumulative risks to multiple stressors. In a given environment, humans and non-human biota are exposed to many of the same chemical and non-chemical stressors. In addition to some shared pathways of exposure, it is possible to identify a common mode(s) of action of some chemical stressors in both humans and wildlife. These commonalities can be used to link human and ecological exposures and responses to multiple stressors in new ways. Benefits of this approach include improving the efficiency and predictive capability of risk assessments to humans and wildlife, especially where there is a common underlying modes-of-action (MOA) or adverse outcome pathway (AOP) of effects. Also, characterization of effects of non-chemical stressors may be enhanced by including ecological endpoints, since the role of abiotic stressors in modulation of toxicity is commonly considered in laboratory and field studies with aquatic and terrestrial organisms. Recommendations on cumulative risk assessment (CRA) put forth in the 2009 NRC Science and Decisions: Advancing Risk Assessment report include development of conceptual models and phased approaches to move these types of assessments forward (NRC 2009). Ecological risk assessment already takes into consideration effects of non-chemical stressors and vulnerabilities (e.g. sensitive habitats, species protection status), recommendations included in the NRC report for advancing cumulative risk assessment for human health. However, there is still a lot to be understood in characterizing ecosystem responses to multiple stressors, such as how multiple stressors alter species response and vulnerability and how this can change ecosystem function/services.

This task will explore new methods for integration of human and ecological endpoints and how these techniques may be applied to CRA. The anticipated impact of projects described under this task is improved assessment of ecosystems and human health through methods for cross-integration. This integration is also anticipated to address community concerns species



regarding environmental and human health impacts and will facilitate the application of CRA to “place-based” assessments.

HHRA Task 6.1 (*RMS ID# HHRA 3.231*) consists of the following four subtasks described briefly below:

- **Subtask 6.1.1. (*RMS ID# HHRA 3.231.1*): Working group for the integration of ecological receptors into the cumulative risk assessment framework**

The purpose of this subtask is to establish a working group of 5 to 10 scientists, agency-wide, with expertise in areas relevant to advancement of cross-species approaches including integration of human and ecological data in cumulative risk assessment (e.g. ecological risk, effects of multiple stressors on aquatic and/or terrestrial biota, toxicology, and tools for integrated assessment). The working group will pursue approaches to advance formal integration of ecological and human health indices and serve as a resource to the Risk Assessment Forum for reviews etc.

- **Subtask 6.1.2. (*RMS ID# HHRA 3.231.2*): Support and application of new tools for integration of human and ecological receptors**

Several new tools developed at the EPA have potential application to enhance the integration of human and ecological receptors. Examples include EPA-Eco-Box being developed by NCEA as a web-based toolbox to provide links to guidance documents, databases, and other relevant information for ecological risk assessors (see HHRA Topic 4 Task 8.4). The Sequence Alignment to Predict Across-Species Susceptibility (SeqAPASS) developed by NHEERL is another example of a web-based tool for addressing the challenges of cross-species extrapolation of chemical toxicity (LaLone et al. 2013). Subtask 6.1.2 is devoted to developing approaches for the application of these tools and characterizing their utility to support CRA. This work will additionally provide support to the other subtasks in Task 6.1 by providing systematic review of evidence in the literature and inferences gained from the tools.

- **Subtask 6.1.3. (*RMS ID# HHRA 3.231.3*): Modeling and multi-criteria decision analysis (MCDA) applications for quantitative integration of human and ecological indicators**

Multi-criteria decision analysis (MCDA) has proven useful for the prioritization of chemical assessments based on integration of different data streams; and also offers transparent valuation providing great utility for informing community assessment (Mitchell et al., 2013; Kiker et al., 2005). Construction of an MCDA computational model



will proceed by formalization of a decision support structure based on the process diagram product of Subtask 6.1.1 and recently introduced exposure modeling concepts such as the Aggregate Exposure Pathway (AEP) proposed as input to the AOP (Teeguarden et al., 2016) that essentially represents a generic conceptual site model (CSM) per the CRA framework (US EPA, 2003), and will be consistent with extant models such as NCEA's Causal Analysis and Diagnosis Decision Information System (CADDIS); all of which support transparent and tractable accounting of valuation of ecological and human health indices. Case studies illustrative of data rich examples as well as those with missing data will be pursued to provide indication of feasibility and identification of significant data gaps. In parallel and closely coupled, this subtask will also pursue further development of a computational sustainability model that was originally started as a Pathfinder Innovation Project (PIP) by NHEERL scientists. The work leverages and additionally informs data integration and approaches for AOP applications in the IRIS inorganic arsenic assessment. The sustainability model will be applied to more data-rich case studies and evaluated for utility to further inform MCDA. All case studies will serve to advance more formal approaches to ecological and human indices, and serve as fodder for the future workshop planned as part of Subtask 6.1.1.

- **Subtask 6.1.4. (RMS ID# HHRA 3.231.4): Multiple stressors in ecological assessments – the case of nitrogen**

The development of the multipollutant Integrated Science Assessment (ISA) for Oxides of Nitrogen and Sulfur-Ecological Criteria (NO_x/SO_x ISA) includes consideration of how multiple chemical and non-chemical (e.g. temperature, climate) stressors affect nitrogen impacts to aquatic and terrestrial ecosystems. Concentration-response relationships of nitrogen with selected ecological assessment endpoints will be evaluated in freshwater systems considering how multiple stressors affect toxicity. Ecological effects of nitrogen deposition to case study areas such as the Sierra Nevada Mountains, Appalachias, Acadia National Park, and/or Rocky Mountain National Park will be evaluated, and ecosystem services of selected impacted biota will be characterized.

Research Approach:

Systematic review and synthesis of current literature on ecological endpoints affected by chemical and non-chemical stressors and/or integration of human and ecological risk assessment will be conducted for the projects under this task. Task 6.1 builds on recommendations of an HHRA vision paper (in final preparation) on opportunities to integrate ecological considerations in CRA and advances in understanding of systems biology to support new applications for qualitative and quantitative approaches. A quantitative model to support sustainability considerations is included in the quantitative approaches. Opportunities identified include conceptual integration based on common or conserved MOA/AOP,



incorporation of the generic ecological assessment endpoints (GEAE) (US EPA 2004) and ecosystem services into CRA, and the use of MCDA to aid problem formulation and transparency of valuation involved when integrating ecological and human health indices.

- **Subtask 6.1.1. (RMS ID# HHRA 3.231.1): Working group for the integration of ecological receptors into the cumulative risk assessment framework**

A working group will be established to develop a standardized working diagram of a conceptual model for use by the EPA that incorporates GEAEs and non-chemical stressors that act on ecological receptors, into the CRA framework. GEAEs have been developed by the EPA for use in risk assessment. This proposed approach will identify receptors and endpoints affected by the stressors while taking into account the effects of non-chemical stressors and needs of stakeholders. This is consistent with the NRC recommendations to develop a conceptual model to advance CRA (NRC 2009). Products under this subtask include formalizing a process diagram for the integration of human and ecological indices and a workshop to convene and consider case studies for application of the tools and approaches developed in other subtasks.

- **Subtask 6.1.2. (RMS ID# HHRA 3.231.2): Support and application of new tools for integration of human and ecological receptors**

Building upon the integration of human health and ecological effects of lead from Lassiter et al (2015), work in this subtask will pursue using SeqAPASS to explore the further integration of human and ecological endpoints by incorporating molecular sequencing data to evaluate cross-species coherence of effects and modes of action. For example, since lead is one of several possible toxicants we may consider for use with SeqAPASS, this subtask could help characterize MOA for ecological effects of lead exposure since there are few such studies. Lead has been demonstrated to affect the IGF-1 pathway in humans and vertebrates and ILS signaling pathway in some invertebrates. Case studies using EPA SeqAPASS tool could be used to predict species that may be susceptible to endocrine disruption by lead by identifying inhibin and IGF-1 like sequences. The feasibility of using EPA-Eco-Box for integration of human and ecological endpoints will be considered once the toolbox is available.

- **Subtask 6.1.3. (RMS ID# HHRA 3.231.3): Modeling and multi-criteria decision analysis (MCDA) applications for quantitative integration of human and ecological indicators**

This subtask will evolve an MCDA computational model based on review and recommendations regarding the process diagram product of Subtask 6.1.1. The initial computational structure will utilize that diagram to modify recent work by Igor Linkov at the US Army Corps of Engineers (US ACE) and then refined in the future with review of case study applications planned for use at the future workshop in that subtask. Collaborations will include (US ACE, input from those involved with the GEAE (subtask



6.1.1), and interaction with NHEERL scientists involved with AOP development and the computational sustainability model for optimization. The computational sustainability model is developing visualization software based on a former PIP project. Comparison of the application and perhaps integration of both types of models to case studies illustrative of data rich examples such as perchlorate or inorganic arsenic as well as those with missing data will be pursued to provide indication of feasibility and identification of significant data gaps.

- **Subtask 6.1.4. (RMS ID# HHRA 3.231.4): Multiple stressors in ecological assessments – the case of nitrogen**

Concentration -response relationships of nitrogen with selected ecological assessment endpoints will be evaluated in freshwater systems considering how multiple stressors affect toxicity. Ecological effects of nitrogen deposition to case study areas such as the Sierra Nevada Mountains, Appalachia, Acadia National Park, and/or Rocky Mountain National Park will be evaluated, and ecosystem services of selected impacted biota will be characterized. At least one peer-reviewed journal article is expected as well as inclusion of concentration-response relationships and impacted ecosystem services associated with specific species in case studies within the NO_x/SO_x ISA-Ecological Criteria.

Task Products:

- **Subtask 6.1.1. (RMS ID# HHRA 3.231.1): Working group for the integration of ecological receptors into the cumulative risk assessment framework**

- **Product 6.1.1.1. (RMS ID# HHRA 3.231.1.1)**
- **Product Title:** Process diagram for organization of human and ecological data integration
- **Contact (email)** [[HYPERLINK "mailto:lassiter.meredith@epa.gov"](mailto:lassiter.meredith@epa.gov)]; [[HYPERLINK "mailto:greaver.tara@epa.gov"](mailto:greaver.tara@epa.gov)]; [[HYPERLINK "mailto:jarabek.annie@epa.gov"](mailto:jarabek.annie@epa.gov)]; [[HYPERLINK "mailto:troyer.michael@epa.gov"](mailto:troyer.michael@epa.gov)]
- **Product Delivery Date:** Q3 FY 2017
- **Product Type:** Process Diagram
- **Product Description:** The current EPA conceptual CRA framework (Figure 6-1) provides for consideration of vulnerability as an integrated function of environmental stressors, physiology and lifestyle; and new advances in understanding of systems biology have elucidated conserved mechanisms resulting in AOPs across species. The purpose of this product is to formalize the previously-developed process diagram for the integration of human and ecological effects from an HHRA vision paper with additional feedback and



discussion to explore refinement and new applications. This process-level diagram will help in organization of additional projects in Task 6.4.

- **Product's Timeline (with milestones):**
 - Q4 FY 2016 Identify agency scientists interested in joining a team focused on integration of ecological receptors in the CRA framework
 - Q2 FY 2018 Draft of the proposed approach including a conceptual diagram based on HHRA vision paper
 - Q4 FY 2018 incorporate feedback from scientists and finalize conceptual approach for the integration of ecological endpoints into CRA efforts
- **Product's intended user/customer/audience:** Agency scientists across programs and regions
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task?** Yes. Deliberations and process diagrams serve to inform other tasks in Project 6.

- **Product 6.1.1.2 (RMS ID# HHRA 3.231.1.2)**
- **Product Title:** Workshop to advance incorporation of ecological risk assessment into cumulative risk assessment frameworks
- **Product Contact (email):** Meredith Lassiter, [[HYPERLINK "mailto:lassiter.meredith@epa.gov"](mailto:lassiter.meredith@epa.gov)]; Tara Greaver, greaver.tara@epa.gov
- **Product's Delivery Date:** Q3 FY 2019
- **Product Type:** Workshop Report
- **Product Description:** Using tools and approaches developed to date as a starting point, this workshop will explore ways to incorporate ecological endpoints into CRA moving from theoretical approaches to practical applications. Scientists with expertise in integration of human health and ecological risk assessment will be invited to participate in the workshop. The purpose of the workshop will be to (1) plan a case study or studies using a site-specific approach to conduct a CRA that incorporates human and ecological endpoints, and (2) identify ways to incorporate GEAE's to case studies
- **Product's Contribution to Output:** Provide a roadmap to move forward with incorporation of ecological endpoints into CRA
- **Product's Timeline (with milestones):**
 - Q3 FY 2017: Develop work assignment through our existing contract with ICF for the workshop
 - Q1 FY 2018: Workshop
 - Q3 FY 2019: Workshop Report
- **Product's intended user/customer/audience:** EPA and risk assessors
- **Is this a key product?** TBD
- **Does this Product contribute to a Product under another Task?** Yes, all tasks in Project 6 would be informed by this roadmap.



Subtask 6.1.2. (RMS ID# HHRA 3.231.2): Demonstration of new tools for integration of human and ecological receptors

- **Product 6.1.2.1. (RMS ID# 3.231.2.1)**
- **Product Title:** Demonstration of new tools for integration of human and ecological receptors
- **Product Contact:** Meredith Lassiter; [[HYPERLINK "mailto:lassiter.meredith@epa.gov"](mailto:lassiter.meredith@epa.gov)]
- **Product's Delivery Date:** Q3 FY2018
- **Product Type:** Journal Manuscript Submission
- **Product's Contribution to Output:** Product will demonstrate how new tools could be applied to further cumulative risk assessment. For example, with SeqAPASS species data may be extrapolated from effects in humans and laboratory animals to other organisms.
- **Product's Timeline (with milestones):**
 - Q2 FY2017: Scoping meeting with scientists at EPA-Duluth
 - Q2 FY 2017: Training in SeqAPASS for one or more scientists in NCEA-RTP
 - Q4 FY 2017: Results from SeqAPASS analysis, scientists will determine if a peer-reviewed publication is a possible product
 - Q4 FY 2017: Feasibility study of this approach using reproductive effects of Pb or another pollutant and endpoint, submission of peer-reviewed journal article, application of EPA-Eco-Box tool as input to CRA efforts.
- **Product's intended user/customer/audience:** Broad scientific audience, especially those interested in tools for cross-species extrapolation
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task?** Yes. Results from these analyses could serve as input to Subtask 6.3 tasks.

Subtask 6.1.3. (RMS ID# HHRA 3.231.3): Modeling and multi-criteria decision analysis (MCDA) applications for quantitative integration of human and ecological indicators

- **Product 6.1.3.1. (RMS ID# HHRA 3.231.3.1)**
- **Product Title:** Multi-criteria decision analysis (MCDA) model application and case studies
- **Product Contact (email):** Annie Jarabek; [[HYPERLINK "mailto:jarabek.annie@epa.gov"](mailto:jarabek.annie@epa.gov)]; (NCEA-RTP)
- **Product's Delivery Date:** Q4 FY 2019
- **Product Type:** MCDA Model application
- **Product Description:** Construction of an MCDA approach and computational model will proceed by formalization of a decision support structure based on the process diagram product of Subtask 6.1.1, in collaboration with Igor Linkov at US ACE, and by utilizing input from extant models such as that developed in Product 6.1.3.2., and CADDIS to support transparent and tractable accounting of valuation of the integration of



ecological and human health indices. Case studies illustrative of data rich examples, as well as those with missing data will be pursued to provide indication of feasibility and identification of significant data gaps and their impact to decisions. The sustainability model will be applied to more data-rich case studies and evaluated for utility to further inform MCDA. All case studies will serve to advance more formal approaches to ecological and human indices, and serve as input for the future workshop planned as part of Subtask 6.1.1.

- **Product's Contribution to Output:** MCDA computational model will provide formal statistical approach for recommendations regarding integration of human and ecological impact indices.
- **Product's Timeline (with milestones):**
 - Development of computational model for application to case studies to inform discussion at workshop: FY2018 Q4
 - Implementation of computational structure and application to case studies
 - Evaluation of application with selected case studies: FY2019 Q4
 - Submission of a manuscript of case studies to a peer-reviewed journal based on feedback (e.g., from workshop planned in Subtask 6.1.1.): FY2019 Q4
 - Recommendations and specification for software development: FY2019 Q4
- **Product's intended user/customer/audience:** Support tool for Agency scientists wishing to integrate human and ecological indices into CRA.
- **Is this a key product?** TBD
- **Does this Product contribute to a Product under another Task?** Yes. Provides formal structure for decision analysis application of recommendations developed in other tasks and interface with Product 6.1.3.2 (RMS ID# HHRA 3.231.3.2) and will be reviewed at the workshop planned in Subtask 6.1.1 (RMS ID# HHRA 3.231.1).
- **Product 6.1.3.2.1. (RMS ID# HHRA 3.231.3.2.1)**
- **Product Title:** Cross-species integration of human health and ecological endpoints into CRA using AEP and AOP: Case study 1 (perchlorate)
- **Product Contact (email):** Stephen Edwards, [[HYPERLINK "mailto:edwards.stephen@epa.gov"](mailto:edwards.stephen@epa.gov)]; David Hines, [[HYPERLINK "mailto:hines.david@epa.gov"](mailto:hines.david@epa.gov)]; Rory Conolly, conolly.rory@epa.gov (NHEERL ISTD); Annie Jarabek, [[HYPERLINK "mailto:Jarabek.annie@epa.gov"](mailto:Jarabek.annie@epa.gov)] (NCEA RTP)
- **Product's Delivery Date:** Q4 FY 2017
- **Product Type:** Journal Manuscript Submission
- **Product Description:** This product will consist of a peer reviewed manuscript outlining a case study that develops an AOP model to integrate ecological and human health endpoints into risk assessment. The case study will describe formation and implementation of a conceptual model that evaluates a conserved AOP across multiple taxa to assess risk in a diverse set of endpoints. Analysis tools that identify sensitive parameters and potentially optimal values for certain parameters will be developed as time permits.



- **Product's Contribution to Output:** This case study may provide the input for the MCDA formal statistical approach used in Product 6.1.3.1 (RMS ID# HHRA 3.231.3.2) for recommendations regarding integration of human and ecological impact indices and the potential to also incorporate benefit:cost considerations.
- **Product's Timeline (with milestones):**
 - Q3 FY 2017 – Completion of conceptual construct for computational model for Case study 1
 - Q3 FY 2018 – Final model for case study 1 (manuscript submission).
- **Product's intended user/customer/audience:** Support tool for Agency scientists wishing to integrate human and ecological indices into CRA.
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task?** Yes. Provides additional valuation optimization to inform Product 6.1.3.1 (RMS ID# HHRA 3.231.3.1) and will also be reviewed at the workshop planned in Subtask 6.1.1. (RMS ID# HHRA 3.231.1). Insights on data integration and AOP applications may inform the IRIS assessment for substances such as inorganic arsenic.
- **Product 6.1.3.2.2. (RMS ID# HHRA 3.231.3.2.2)**
- **Product Title:** Cross-species integration of human health and ecological endpoints into CRA using AEP and AOP: Case study 2
- **Product Contact (email):** Stephen Edwards, [[HYPERLINK "mailto:edwards.stephen@epa.gov"](mailto:edwards.stephen@epa.gov)]; David Hines, [[HYPERLINK "mailto:hines.david@epa.gov"](mailto:hines.david@epa.gov)]; Rory Conolly, conolly.rory@epa.gov (NHEERL ISTD); Annie Jarabek (NCEA RTP), jarabek.annie@epa.gov
- **Product's Delivery Date:** Q4 FY 2018
- **Product Type:** Journal Manuscript Submission
- **Product Description:** This product will consist of a peer reviewed manuscript describing a second case study that uses AOP models to integrate ecological and human health endpoints into risk assessment. This second case study will present an AOP-based conceptual model for risk from a different chemical than the substance examined in case study 1 (Product 6.1.3.2.1; RMS ID# 3.231.3.2.1) and apply this model to evaluate risk across human health and ecological endpoints. Case study 2 will serve to further develop the application of AOPs to risk assessment, and will demonstrate the breadth of applicability of the AOP concept in this field.
- **Product's Contribution to Output:** This case study may be used as the input to an MCDA approach (Product 6.1.3.1; RMS ID# HHRA 3.231.3.2) to provide formal statistical recommendations regarding integration of human and ecological impact indices.
- **Product's Timeline (with milestones):**
 - Q2 FY 2018 –Development of computational approach for Case study 2
 - Q4 FY 2018 – Application of model for case study 2 (manuscript submission). White paper discussing how this modeling work could be integrated with the other MCDA tools developed within the task.



- **Product's intended user/customer/audience:** Support tool for Agency scientists wishing to integrate human and ecological indices into CRA.
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task?** Yes. Provides additional valuation optimization to inform Product 6.1.3.1 (RMS ID# HHRA 3.231.3.1) and will also be reviewed at the workshop planned in Subtask 6.1.1. (RMS ID# HHRA 3.231.1). Insights on data integration and AOP applications may inform the IRIS assessment for substances such as inorganic arsenic.

Subtask 6.1.4. (RMS ID# HHRA 3.231.4): Multiple stressors in ecological assessment – the case of nitrogen

- **Product Title:** Multiple stressors in ecological assessment – the case of nitrogen
- **Product Contact (email):** [[HYPERLINK "mailto:greaver.tara@epa.gov"](mailto:greaver.tara@epa.gov)], lassiter.meredith@epa.gov
- **Product's Delivery Date:** Q4 FY 2017
- **Product Type:** Journal Manuscript Submission
- **Product Description:** Concentration-response relationships of nitrogen with selected ecological assessment endpoints will be evaluated in freshwater systems considering how multiple stressors affect toxicity. Ecological effects of nitrogen deposition to case study areas such as the Sierra Nevada Mountains, Appalachia, Acadia National Park, and/or Rocky Mountain National Park will be evaluated, and ecosystem services of selected impacted biota will be characterized. At least one peer-reviewed journal article is expected as well as inclusion of concentration-response relationships and impacted ecosystem services associated with specific species in case studies within the NOx/SOx ISA.
- **Product's Contribution to Output:** Characterization of how concentration-response relationships of nitrogen are affected by multiple stressors will provide insights into incorporating ecological endpoints in cumulative risk frameworks. Links between deposition of nitrogen, the role of multiple stressors, and changes to ecosystem services will be demonstrated through impacts to specific species.
- **Product's Timeline (with milestones):**
 - Q1FY 2016- Conduct a literature search and identify papers with concentration-response relationships of nitrogen to ecological endpoints
 - Q2FY 2016- Extract dose-response data from relevant literature
 - Q3FY 2016- Conduct analyses of concentration-response relationships for NOx/SOx ISA-Ecological Criteria
 - Q4FY 2017- Submission of a manuscript to a peer-reviewed journal
- **Product's intended user/customer/audience:** OAQPS and broader scientific audience
- **Is this a key product?** TBD
- **Does this Product contribute to a Product under another Task?** Yes, production of ISAs in Project 3, Task 3.1 (RMS ID# HHRA 2.211) as well as inform other subtasks in this task.



Task Dependencies: Work on the models in Subtask 6.1.3 requires establishing an IAG with US ACE and the hire of an R-authority postdoc, both are underway but may result in delays.

Task Constraints:

- **Scientific:**
 - The assessment of cumulative risk for ecological receptors is constrained by the available information on receiving biota. There are many organisms for which no toxicity data exist and assessments rely on extrapolation of effects from other species. The complexity of considering multiple co-occurring stressors is a constraint especially considering multiple environmental compartments (i.e. soil, water, biota) and non-chemical stressors in natural systems
 - **Resources:** Work on all subtasks in this task is constrained by competing priorities and the availability of EPA staff and ORISE support has been included in the budget for this project

Task Quality Assurance and Data Management Needs: All subtasks in Task 6.1 are covered as follows:

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status.
 - NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 to Develop Methods, Tools, Models and Supporting Analysis.
 - Additionally, Product 6.1.3.2 (*RMS ID# HHRA 3.231.3.2*) is covered as follows: IRP-NHEERL/ISTD/SBB/WL/2012-01-r0 (This QAPP is currently under revision and will be transferred to one of the existing mentors upon the arrival of the new postdoc)
- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
 - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) for Extraction of Scientific Data into the Health and Environmental Research Online (HERO) Database System
 - Additionally, Product 6.1.3.2 (*RMS ID# HHRA 3.231.3.2*) is covered as follows: This will be dependent on the specific case studies chosen for the product to be determined after the postdoc has arrived and will likely also use the HERO resource per above.



References:

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Lassiter MG, Owens EO, Patel MM, Kirrane E, Madden M, Richmond-Bryant J, Hines EP, Davis JA, Vinikoor-Imler L, Dubois JJ. (2015). Cross-species coherence in effects and modes of action in support of causality determinations in the U.S. Environmental Protection Agency's Integrated Science Assessment for Lead. *Toxicol* 1;330, 19 – 40.

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NRC (2009). Science and decisions: Advancing risk assessment. Chapter 7. Implementing cumulative risk assessment. Committee on improving risk analysis approaches used by the US EPA; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies. National Academies Press: Washington, DC. [[HYPERLINK "http://dels.nas.edu/dels/rpt_briefs/IRA_brief_final.pdf"](http://dels.nas.edu/dels/rpt_briefs/IRA_brief_final.pdf)].

Teeguarden JG, Tan YM, Edwards SM, Leonard, JA, Anderson KA, Corley RA, Kile ML, Simonich SM, Stone D, Tanguay RL, Waters KM, Harper SL, William DE (2016). Completing the link between exposure science and toxicology for improved environmental health decision making: The aggregate exposure framework. *Environ Sci Technol.* May 3;50(9):4579-86.

U.S. EPA. (2003). Framework for Cumulative Risk Assessment. PA/630/P-02/001A. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum, Office of Research and Development. <http://nepis.epa.gov/>, [[HYPERLINK "http://www.epa.gov/raf/publications/framework-cra.htm"](http://www.epa.gov/raf/publications/framework-cra.htm)].

U.S. EPA. (2004). Generic Ecological Assessment Endpoints (GEAEs) for Ecological Risk Assessment. EPA/630/P-02/004F. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum, Office of Research and Development.



Task Resources:

- **Subtask 6.1.1. (RMS ID# HHRA 3.231.1): Working group for the integration of ecological receptors into the cumulative risk assessment framework**

Extramural Resources

Lab or Center receiving money: NCEA

Division: RTP

Contact name: Meredith Lassiter

Extramural (NPD RAP) in \$K

- FY16: \$0K
- FY17: \$0K
- FY18: \$80K
- FY19: \$0K

Description of Extramural needs for each FY: Workshop to review case studies developed in Subtask 6.1.3.3 and develop recommendations regarding advancing ecological and human integration.

Description of impact on Product delivery (or contribution) if resources are not available in a timely manner? Timetable has been adjusted to accommodate key NCEA scientists competing priorities in the ISA program.

Proposed method for Extramural Need: Contract to support workshop logistics.

Intramural Resources

Intramural (L/C Corporate) in \$K (NHEERL): N/A

Special Resource Needs and Considerations

Special facilities or equipment needed: N/A

Intramural Resources

Intramural (L/C Corporate) in \$K: N/A

Description of Intramural Needs for each FY: N/A

Special Resource Needs and Considerations



Special facilities or equipment needed: N/A

Subtask 6.1.1. (RMS ID# HHRA 3.231.1) Staffing:

Staff Member	L/C	Division	Expertise	Contribution to Subtask	FY16 % FTE	FY17 % FTE	FY18 % FTE	FY19 % FTE
Product								
6.1.3.1								
Meredith Lassiter	NCEA	RTP	Ecologist	Task & Subtask Manager	5	10	10	
Tara Greaver	NCEA	RTP	Ecologist		5	10	10	
Michael Troyer	NCEA	CIN	Ecologist	GEAE expert	5	5	5	5
Annie Jarabek	NCEA	RTP	Toxicology, decision analysis	Vision paper lead; AOP application	5	5	5	5
Others TBD								

- **Subtask 6.1.2. (RMS ID# HHRA 3.231.2): Support and application of new tools for integration of human and ecological receptors**

Extramural Resources

Lab or Center receiving money: NCEA

Division: RTP

Contact name: Meredith Lassiter

Extramural (NPD RAP) in \$K

- FY16: \$0K
- FY17: \$0K
- FY18: \$0K
- FY19: \$0K

Description of Extramural needs for each FY: N/A

Description of impact on Product delivery (or contribution) if resources are not available in a timely manner? Timetable has been adjusted to accommodate key NCEA scientists competing priorities in the ISA program.



Proposed method for Extramural Need: NHEERL MOU

Intramural Resources

Intramural (L/C Corporate) in \$K: N/A

Special Resource Needs and Considerations

Special facilities or equipment needed: N/A

Intramural Resources

Intramural (L/C Corporate) in \$K: N/A

Description of Intramural Needs for each FY: N/A

Special Resource Needs and Considerations

Special facilities or equipment needed: N/A

Subtask 6.1.2. (RMS ID# HHRA 3.231.2) Staffing:

Staff Member	L/C	Division	Expertise	Contribution to Subtask	FY16 % FTE	FY17 % FTE	FY18 % FTE	FY19 % FTE
Product								
6.1.3.2								
Meredith Lassiter	NCEA	RTP	Ecologist	Task & Subtask Manager	5	10	10	
Carlie Malone*	NHEER	MED	Ecologist	SeqAPASS consultation	NA			
Erin Hines	NCEA	RTP	Toxicologist	Toxicology consultation	5	5		

*Collaborator

Subtask 6.1.3. (RMS ID# HHRA 3.231.3): Modeling and multi-criteria decision analysis (MCDA) applications for quantitative integration of human and ecological indicators

- **Product 6.1.3.2. (RMS ID# HHRA 3.231.3.2): Computational Sustainability Model**

Extramural Resources



Lab or Center receiving money: NCEA

Division: RTP

Contact name: Annie Jarabek

Extramural (NPD RAP) in \$K

- FY16: 0
- FY17: 0
- FY18: 65
- FY19: N/A

Description of Extramural needs for each FY: Modification of MCDA model to implement conceptual process diagram (25K); application to n = 3 case studies (15K each); implementation of any refinement based on workshop recommendations (10K) as needed

Description of impact on Product delivery (or contribution) if resources are not available in a timely manner? Timetable for model development will be delayed.

Proposed method for Extramural Need: Interagency agreement with US ACE

Intramural Resources

Intramural (L/C Corporate) in \$K (NHEERL): N/A

Special Resource Needs and Considerations

Special facilities or equipment needed: N/A

- **Product 6.1.3.2. (RMS ID# HHRA 3.231.3.2): Cross-species integration of human health and ecological endpoints into CRA using AEP and AOP**

Extramural Resources

Lab or Center receiving money: NHEERL

Division: ISTD

Contact name: Stephen Edwards

Extramural (NPD RAP) in \$K

- FY16: 100K
- FY17: 100K
- FY18: 0K
- FY19: 0K



Description of Extramural needs for each FY: R-authority postdoc for modeling

Description of impact on Product delivery (or contribution) if resources are not available in a timely manner? Timetable for model development will be delayed.

Proposed method for Extramural Need: R-authority postdoc

Intramural Resources

Intramural (L/C Corporate) in \$K (NHEERL)

- FY16: \$2K
- FY17: \$2K
- FY18: \$2K
- FY19: 0K

Description of Intramural Needs for each FY: Computer supplies and software
This product will be entirely modeling based, so no major costs are anticipated.

Special Resource Needs and Considerations

Special facilities or equipment needed: N/A

Subtask 6.1.3. (RMS ID# HHRA 3.231.3) Staffing:

Staff Member	L/C	Division	Expertise	Contribution to Subtask/Product	FY16 % FTE	FY17 % FTE	FY18 % FTE	FY19 % FTE
Product 6.1.3.1								
Annie Jarabek	NCEA	RTP	Toxicology, decision analysis	Subtask and product lead	0	0	10	10
Product 6.1.3.2.								
Annie Jarabek	NCEA	RTP	Toxicology, decision analysis	Subtask and product lead	10	10	10	
Stephen Edwards	NHEERL	ISTD	Systems Biology	Co-mentor postdoc	10	5	0	
Rory Conolly	NHEERL	ISTD	Computational Modeling	Co-mentor postdoc	10	10	10	
R Authority postdoc (David Hines)	NHEERL	ISTD	Applied mathematics/computational modeling	Develop models, analyze data, write manuscripts	100	100	100	



- **Subtask 6.1.4. (RMS ID# HHRA 3.231.4): Multiple stressors in ecological assessments – the case of nitrogen**

Extramural Resources

Lab or Center receiving money: NCEA

Division: RTP

Contact name: Tara Greaver

Extramural (NPD RAP) in \$K

- FY16: OK
- FY17: OK
- FY18: OK
- FY19: OK

Description of Extramural needs for each FY: N/A

Description of impact on Product delivery (or contribution) if resources are not available in a timely manner? Timetable will be adjusted to accommodate key NCEA scientists with competing priorities in the ISA program.

Proposed method for Extramural Need: N/A

Intramural Resources

Intramural (L/C Corporate) in \$K (NHEERL): N/A

Special Resource Needs and Considerations

Special facilities or equipment needed: N/A

Intramural Resources

Intramural (L/C Corporate) in \$K: N/A

Description of Intramural Needs for each FY: N/A

Special Resource Needs and Considerations

Special facilities or equipment needed: N/A

Subtask 6.1.4. (RMS ID# HHRA 3.231.4) Staffing:



Staff Member	L/C	Division	Expertise	Contribution to Subtask/Product	FY16 % FTE	FY17 % FTE	FY18 % FTE	FY19 % FTE
Product								
6.1.3.4								
Tara Greaver	NCEA	RTP	Ecologist	Subtask & product lead	5	10	10	
Meredith Lassiter	NCEA	RTP	Ecologist	Ecologist	5	5	5	



Task 6.2

(RMS ID# HHRA 3.232)

Incorporating Multiple Stressors

Task Lead (TL): Glenn Rice (NCEA CIN)

Task Start Date: 10/01/2015

Task End Date: 09/30/2019

Task Description:

Under Task 6.2, the HHRA Program will continue to develop Cumulative Risk Assessment (CRA) methods and case studies that evaluate exposures, assess dose-response, and characterize risks posed by multiple chemical and non-chemical stressors to human health. The types of stressors envisioned for consideration in CRAs include biological agents, physical entities such as temperature, and psychosocial stressors, in addition to hazardous environmental chemicals. Expert panels have encouraged EPA to expand the focus of human health risk assessment, moving from analyses of human health risks posed by individual environmental stressors toward CRA (NAS, 2008; 2009; USEPA, 2003); however, progress in this area of risk assessment is limited by the lack of methods to support such comprehensive investigations that examine health outcomes associated with the combined effects of multiple stressors.

To accomplish this work of methods development and then application in case studies, Task 6.2. (RMS ID# HHRA 2.232.2) is composed of two subtasks as follows:

- **Subtask 6.2.1 (RMS ID# HHRA 3.232.1): Cumulative Risk Assessment Methods for Integrating Stressors**
Under this subtask, HHRA scientists will continue to lead the development of cumulative risk assessment (CRA) methods that 1) inform hazard assessment/characterization; 2) evaluate exposures; 3) assess dose-response; and 4) characterize risks posed by multiple chemical and non-chemical stressors to human health.
- **Subtask 6.2.2 (RMS ID# HHRA 3.232.2): Cumulative Risk Assessment – Multiple Stressor Case Studies**
Research indicates that nonchemical stressors can interact and modify the response to chemical toxicants. However, the extent to which nonchemical stressors modify toxic responses is not known. In addition, the mechanisms involved in their interaction is only beginning to be understood. This subtask presents case studies of chemical and nonchemical stressors in an attempt to better understand how nonchemical stressors



may increase vulnerability of individuals or communities to toxicant exposures. Ultimately, these case studies should improve our ability to assess multiple stressors in cumulative risk assessment.

Research Approach:

Work under the two subtasks will be conducted in concert to advance CRA methods and illustrate their application in case studies. Methods will mature with additional research and benefit from lessons learned in the case studies. Existing epidemiological and toxicological study data will be accessed for the purpose of developing CRA methods and case study applications. Case studies will explore specific interactions among established stressors. The development of case studies that include disparate types of stressors (e.g., chemical and non-chemical) will be emphasized. Non-chemical stressors with similar health endpoints and mechanisms of action to chemical stressors will be prioritized for case studies. As needed, experts will be convened in workshops to inform issues relevant to CRA approaches.

- **Subtask 6.2.1 (RMS ID# HHRA 3.232.1): Cumulative Risk Assessment Methods for Integrating Stressors**
- **Subtask 6.2.2 (RMS ID# HHRA 3.232.2): Cumulative Risk Assessment – Multiple Stressor Case Studies**

Task Constraints:

- **Subtask 6.2.1 (RMS ID# HHRA 3.232.1): Cumulative Risk Assessment Methods for Integrating Stressors.** Specific products developed under this subtask will be of interest to select EPA program offices, so their timely review of these relevant products will be needed. Sufficient funding of vehicle for external scientists' contributions to workshop. Sufficient funding for ASPPH and ORISE Fellows. Commitment of FTE and availability of EPA staff given multiple and sometimes competing priorities.
- **Subtask 6.2.2 (RMS ID# HHRA 3.232.2): Cumulative Risk Assessment – Multiple Stressor Case Studies.** Specific products developed under this subtask will be of interest to select EPA program offices; their timely review of these relevant products will be needed. Sufficient funding of vehicle for external scientists' contributions to workshop. Sufficient funding for ASPPH and ORISE Fellows. Commitment of FTE and availability of EPA staff given multiple and sometimes competing priorities.



Task Dependencies:

Subtask 6.2.1 (RMS ID# HHRA 3.232.1): Cumulative Risk Assessment Methods for Integrating Stressors. Efficient Internal Review and Clearance processes.

Subtask 6.2.2 (RMS ID# HHRA 3.232.2): Cumulative Risk Assessment – Multiple Stressor Case Studies. Efficient Internal Review and Clearance processes.

Task Quality Assurance and Data Management Needs:

Subtask 6.2.1 (RMS ID# HHRA 3.232.1): Cumulative Risk Assessment Methods for Integrating Stressors

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status. Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 To Develop Methods, Tools, Models and Supporting Analysis
- Will this Task involve large amounts of data that need a data management plan? If yes, explain TBD.

Subtask 6.2.2 (RMS ID# HHRA 3.232.2): Cumulative Risk Assessment – Multiple Stressor Case Studies

- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status. Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 To Develop Methods, Tools, Models and Supporting Analysis
- Will this Task involve large amounts of data that need a data management plan? If yes, explain TBD.

Task Products:

Subtask 6.2.1 (RMS ID# HHRA 3.232.1): Cumulative Risk Assessment Methods for Integrating Stressors

- **Product 6.2.1.1 (RMS ID# HHRA 3.232.1.1)**
- **Product Title:** Characterizing Risk for Cumulative Risk Assessment (CRA)
- **Product Contact (email):** Glenn Rice (rice.glenn@epa.gov)
- **Product's Delivery Date:** 9/30/16



- **Product Description: Journal Manuscript Submission**
This manuscript describes elements of and considerations for the risk characterization step for CRAs. The risk characterization step of a CRA can be much more difficult than its counterpart in “conventional” single stressor risk assessments. The manuscript will utilize a series of examples to illustrate some of these difficulties (e.g., development of dose-response functions for joint stressor exposure) and identify some methods for scientifically addressing these difficulties in the risk characterization step of a CRA.
- **Product’s Contribution to Output:** This manuscript describes elements of and considerations for the risk characterization step for CRAs that can be used by regional and program office risk assessors in the EPA.
- **Product’s Timeline (with milestones):**
 - Final Draft Journal Manuscript to Coauthors: 12/30/15
 - Journal Manuscript Internal Review and EPA Clearance: 4/1/16
 - Journal Manuscript Submission: 9/30/16
- **Product’s intended user/customer/audience:** Regional and Program office risk assessors (accessible to scientists and managers)
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task?** If so, identify other Task. No.
- **Product 6.2.1.2 (RMS ID# HHRA 3.232.1.2)**
- **Product Title: Grouping stressors for human health cumulative risk assessments: A simplifying approach for inclusion of non-chemical stressors and vulnerabilities**
- **Product Contact (email):** Glenn Rice (rice.glenn@epa.gov)
- **Product’s Delivery Date:** 12/20/18
- **Product Description: Journal Manuscript Submission**
Consensus is growing on the need to assess some environmental health risks with cumulative risk assessment (CRA) approaches that examine health outcomes associated with the combined effects of multiple stressors and consider vulnerabilities. This manuscript extends an earlier grouping approach focused on grouping of chemical stressors based on exposure and health effects information. The extended CRA groupings approach provides methods for grouping and integrating chemical and non-chemical stressors including potential vulnerabilities due to immutable factors, diseases and physiologic states affecting health risks. Development of the manuscript will entail secondary data analyses of epidemiology and toxicology data and refinement of an existing EPA approach described in EPA’s (2007) “Concepts, Methods, and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document.”
Product’s Contribution to Output: Approaches are needed to efficiently evaluate CRA information.



- Product's Timeline (with milestones):
 - Final Draft Journal Manuscript to Coauthors: 11/21/17
 - Journal Manuscript Internal Review and EPA Clearance: 9/15/18
 - Journal Manuscript Submission: 12/20/18
- Product's intended user/customer/audience: Regional and Program office risk assessors (accessible to scientists and managers)
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? If so, identify other Task. No.

- **Product 6.2.1.3 (RMS ID# HHRA 3.232.1.3)**

- **Product Title: Causal Inference in Cumulative Risk Assessment: The Role of Directed Acyclic Graphs**

- Product Contact (email): Beth Brewer (brewer.beth@epa.gov)
- Product's Delivery Date: 9/1/2016
- Product Description: Journal Manuscript Submission

As noted in the National Academy of Science's Science and Decisions (2009), one of the challenges EPA is grappling with is the ability to examine multiple exposures (including complex mixtures) and vulnerability of exposed populations in a cumulative risk assessment (CRA) perspective. They also noted a distinct need in CRA to develop methods to address the integration of non-chemical stressors into cumulative risk assessment. This task focuses on challenges to address these needs including development of case studies and methodology to integrate multiple (chemical and non-chemical) stressors into CRA.

This manuscript addresses the potential use of directed acyclic graphs (DAGs) for CRA applications. It focuses on DAGs as a tool for planning and scoping, risk analysis and risk characterization phases of a CRA. The manuscript describes the theoretical underpinnings of DAGs and provides useful guidance on their consideration for CRAs. The relationship between conceptual models and DAGs was explored for each phase of a hypothetical CRA. DAGitty.net software was used to develop a DAG for comparison with a conceptual model and to better delineate causal pathways. This tool should help inform causal assessment and improve weight of evidence considerations.

- Product's Contribution to Output: This manuscript will offer some guidance on how to use DAGs to inform the CRA process which can be used by regional and program office risk assessors in the EPA and beyond
- Product's Timeline (with milestones):
 - Final Draft Journal Manuscript to Coauthors: 3/28/16
 - Journal Manuscript Internal Review and EPA Clearance: 6/1/16
 - Journal Manuscript Submission: 9/1/16 [Submitted: 3/15/16]



- Product's intended user/customer/audience: Regional and Program office risk assessors (accessible to scientists and managers)
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? If so, identify other Task. No.

- **Product 6.2.1.4 (RMS ID# HHRA 3.232.1.4)**
- **Product Title: A Review of STAR Research Grants Exploring the Role of Nonchemical Stressors in Cumulative Risk Assessments.**
- Product Contact (email): Deborah Segal ([[HYPERLINK "mailto:segal.deborah@epa.gov"](mailto:segal.deborah@epa.gov)]); Maggie Breville (Breville.maggie@epa.gov).
- Product's Delivery Date: 9/30/18
- Product Description: Journal Manuscript Submission
 - This manuscript synthesizes the research results for grants funded through the EPA STAR RFA "Understanding the Role of Nonchemical Stressors and Developing Analytic Methods for Cumulative Risk Assessments" and represents a collaboration between the Sustainable and Healthy Communities (SHC) and HHRA research programs. This project will be conducted in collaboration with the NCER Project Officer (Maggie Breville) for the grants, who will also be lead author, as well as with the grantees. The manuscript will discuss the implications of the findings to cumulative risk assessments and lessons learned on utilizing a community participatory approach. Seven grants were initially funded in 2010 to explore the biological underpinning of the interaction of nonchemical stressors with toxic chemicals and also to develop statistical methods for the incorporation of nonchemical stressors into cumulative risk assessments. Some of the subsequent publications of the grantees will be reviewed, as well their annual progress reports. Product's Contribution to Output: This manuscript will highlight how nonchemical stressors can exacerbate chemical toxicity and how this information can be considered in cumulative risk assessments.
- Product's Timeline (with milestones):
 - Final Draft Journal Manuscript to Coauthors: 5/1/18
 - Journal Manuscript Internal Review and EPA Clearance: 7/1/18
 - Journal Manuscript Submission: 9/30/18
- Product's intended user/customer/audience: Regional and Program office risk assessors (accessible to scientists and managers)
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? If so, identify other Task. No.



Subtask 6.2.2 (RMS ID# HHRA 3.232.2): Cumulative Risk Assessment – Multiple Stressor Case Studies

- **Product 6.2.2.1 (RMS ID# HHRA 3.232.2.1):**
- **Product Title: Analyzing greenspace and allergy occurrence from a Cumulative Risk Assessment (CRA) perspective**
- Product Contact (email): Glenn Rice (rice.glenn@epa.gov)
- Product's Delivery Date: 1/4/2018
- Product Description: Journal Manuscript Submission
Greenspace is defined as publicly accessible land that is at least partially vegetated. In children and adults, greenspace has been associated with health effects related to improved air quality, increased physical activity, and psychosocial improvements. Health benefits or risks of greenspace on allergy development in children have not been thoroughly investigated. This product entails the development of a manuscript that investigates the incorporation of greenspace measures into analyses of environmental exposure and potential health impacts in an epidemiologic cohort study of children.
Development of the manuscript will entail analyses of cohort data (allergy; residential locations), and development of spatial analytic methods to derive greenspace exposure estimates.
- Product's Contribution to Output: This manuscript describes an analysis of access to greenspace, exposure to motor vehicle exhaust and allergy occurrence from a CRA perspective.
- Product's Timeline (with milestones):
 - Final Draft Journal Manuscript to Coauthors: 4/21/17
 - Journal Manuscript Internal Review and EPA Clearance: 7/31/17
 - Journal Manuscript Submission: 1/4/18
- Product's intended user/customer/audience: Regional and Program office risk assessors (accessible to scientists and managers)
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? If so, identify other Task. No.
- **Product 6.2.2.2. (RMS ID# HHRA 3.232.2.2):**
- **Product Title: Workgroup Report: Greenspace (GS) exposure and health effect occurrence from a Cumulative Risk Assessment (CRA) perspective**
- Product Contact (email): Glenn Rice ([[HYPERLINK "mailto:rice.glenn@epa.gov"](mailto:rice.glenn@epa.gov)])
- Product's Delivery Date: 10/15/16
- Product Description: EPA Workgroup Report
Product's Contribution to Output: The product represents a report of a workshop that explored the various greenspace measures and the epidemiologic evidence of associations between greenspace exposures and various health outcomes and 2)



developing an EPA summary of the workshop findings. This workshop report will summarize the results of an EPA-led workshop that will address greenspace exposure measures, associations with health outcomes and consider these interactions as opportunities for CRA methods to be developed.

- Product's Timeline (with milestones):
 - Final Draft WS Report to Coauthors: 12/15/15
 - Internal Review and EPA Clearance: 4/16/16
 - Submission of Workshop Report for posting on EPA website: 10/15/16
 - Project Finalized (6/30/16). URL for Report
<https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=314417>
- Product's intended user/customer/audience: Regional and Program office risk assessors, risk managers, city planners, etc (accessible to scientists and managers);
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? If so, identify other Task. No.

- **Product 6.2.2.3. (RMS ID# HHRA 3.232.2.3):**

- **Product Title: Cumulative risk assessment considerations for chronic kidney disease**

- Product Contact (email): Yu-Sheng Lin, Lin.Yu-Sheng@epa.gov
- Product's Delivery Date: June 30, 2018
- Product Description: Peer-reviewed Journal submission

The goal of the proposed project is to develop predictive models for the interaction of chemical and other non-chemical stressors, illustrated by a specific example of chemical nephrotoxicity. Chronic kidney disease is associated with exposure to multiple metals (e.g., cadmium, lead, and mercury) and non-chemical (e.g., diabetes), but limited epidemiological studies to date have assessed the combined effects of both chemical and non-chemical stressors on chronic health in the context of cumulative risk assessment. The approach developed in this proposal (e.g., statistical models, see below) has potential to be applied to other U.S. populations exposed to these multiple stressors in order to identify high-risk populations and inform regulatory policy.

The proposed project will develop conceptual data models (e.g., structural equation models along with directed acyclic graphs) using the data from national databases (e.g., NHANES datasets) to evaluate the combined impact of metal stressors (lead, cadmium, and mercury) and non-chemical risk factors (e.g., socioeconomic status and diabetes, elevated BMI, and other risk factors) on two major prognostic indicators of kidney disease (e.g., reduced glomerular filtration rate and albuminuria), and later renal-relevant mortality (e.g., renal cancer). For example, structural equation models will be applied to investigate complex associations



- among predictors of stressors as well as adverse health outcomes (e.g., albuminuria prevalence using cross-sectional analysis).
- Product's Timeline (with milestones):
 - Manuscript to coauthors 1/31/2016 for initial review;
 - Manuscript to Management 3/31/2018;
 - Manuscript ready for submission to peer-reviewed journal 6/30/2018
- Product's Contribution to Output:

The USEPA has been increasingly considering other non-chemical stressors that may be risk factors for adverse health outcomes or effect measure modifiers. A better understanding of the interactions between the chemical of interest and those stressors could help elucidate the key sources of variability in susceptibility in dose-response analyses.
- Product's intended user/customer/audience: (i) NCEA assessments; (ii) Office of Children's Health Protection and other EPA program offices; (iii) Public at large
- Is this a key product? No
- Does this Product contribute to a Product under another Task? If so, identify other Task. No.

Task Resources:

Subtask 6.2.1 (RMS ID# HHRA 3.232.1): Cumulative Risk Assessment Methods for Integrating Stressors.

Product 6.2.1.1. (RMS ID# HHRA 3.232.1.1):

Extramural Resources

Lab or Center receiving money: NCEA

Division: Cincinnati

Contact name: Glenn Rice

Extramural (NPD RAP) in \$K: 0 – FTE only

Description of Extramural needs for each FY: To compensate the anticipated technical contributions of several scientists outside of EPA, who will contribute to the manuscript

Description of impact on Product delivery (or contribution) if resources are not available in a timely manner: A delay might reduce EPA's ability to effectively characterize cumulative risks.

Proposed method for Extramural Need: Interagency Agreement between the EPA's Risk Assessment Forum and Argonne National Laboratory

Intramural Resources

Intramural (L/C Corporate) in \$K

Description of Intramural Needs for each FY

Special Resource Needs and Considerations

Special facilities or equipment needed: N/A

Product 6.2.1.1. Staffing:

Staff Member	L/C	Division	Expertise	Contribution to Product	FY16 % FTE	FY17 % FTE	FY18 % FTE
J. Michael Wright	NCEA	CIN	Epidemiology/CRA	Co-author	5	5	--
Glenn E. Rice	NCEA	CIN	Risk Assessment/CRA	Co-author	10	5	--

Product 6.2.1.2 (RMS ID# HHRA 3.232.1.2)Extramural Resources

Lab or Center receiving money: NCEA

Division: CIN

Contact name: Glenn Rice

Extramural (NPD RAP) in \$K: None

Description of Extramural needs for each FY: N/A

Description of impact on Product delivery (or contribution) if resources are not available in a timely manner: N/A

Proposed method for Extramural Need: Interagency Agreements; between the EPA's Risk Assessment Forum and Argonne National Laboratory

Intramural Resources

Intramural (L/C Corporate) in \$K: None

Special Resource Needs and Considerations



Special facilities or equipment needed: N/A

Product 6.2.1.2. (RMS ID# HHRA 3.232.1.2): Task Staffing

Staff Member	L/C	Division	Expertise	Contribution to Product	FY16 % FTE	FY17 % FTE	FY18 % FTE
J. Michael Wright	NCEA	CIN	Epidemiology/CRA	Co-author	-	5	5
Glenn E. Rice	NCEA	CIN	CRA/Risk Assessment	Co-author	5	10	5

Product 6.2.1.3 (RMS ID# HHRA 3.232.1.3)

Extramural Resources

Lab or Center receiving money: NCEA

Division: CIN

Contact name: Beth Brewer

Extramural (NPD RAP) in \$K: None – staff FTE only (see below)

Description of Extramural needs for each FY: N/A

Description of impact on Product delivery (or contribution) if resources are not available in a timely manner?

Proposed method for Extramural Need: N/A

Intramural Resources

Intramural (L/C Corporate) in \$K: None

Description of Intramural Needs for each FY: N/A

Special Resource Needs and Considerations

Special facilities or equipment needed: N/A

Product 6.2.1.3 (RMS ID# HHRA 3.232.1.3) Staffing:

Staff Member	L/C	Division	Expertise	Contribution to Product	FY16 % FTE	FY17 % FTE	FY18 % FTE
Beth Brewer*	OSA	DC	CRA	Lead Author	NA	NA	--



J. Michael Wright	NCEA	CIN	Epidemiology/CR A	Co-author	10	5	--
Glenn Rice	NCEA	CIN	CRA/Risk Assessment	Co-author	10	5	--
Lucas Neas*	NHEERL	RTP	Epidemiology	Co-author	NA	NA	--

*Collaborator

Product 6.2.1.4 (RMS ID# HHRA 3.232.1.4)

Extramural Resources

Lab or Center receiving money: NCEA
Division: Washington
Contact name: Deborah Segal

Extramural (NPD RAP) in \$K: None— staff FTE only (see below):

Description of Extramural needs for each FY: N/A

Description of impact on Product delivery (or contribution) if resources are not available in a timely manner: A delay might slow EPA's ability to efficiently conduct CRAs that utilize epidemiological evidence supporting differential risk associated with multiple sources of vulnerability

Proposed method for Extramural Need: N/A

Intramural Resources

Intramural (L/C Corporate) in \$K: None

Description of Intramural Needs for each FY: N/A

Special Resource Needs and Considerations

Special facilities or equipment needed: N/A

Product 6.2.1.4 (RMS ID# HHRA 3.232.1.4) Staffing:

Staff Member	L/C	Division	Expertise	Contribution to Product	FY16 % FTE	FY17 % FTE
Deborah Segal	NCEA	W	CRA/Toxicology	Co-author	5	10
Maggie Breville*	NCER	DC	SHC/Grant Management	Lead Author	NA	NA

*Collaborator



Subtask 6.2.1. (RMS ID# HHRA 3.232.1) Summary

Subtask 6.2.1. (RMS ID# HHRA 3.232.1) Extramural Resources Summary: N/A

Subtask 6.2.1. (RMS ID# HHRA 3.232.1) Staffing Summary

Staff Member	L/C	Div	Expertise	Contribution	FY16 % FTE	FY17 % FTE	Product
J. Michael Wright	NCEA	CIN	Epidemiology/CRA	Co-author	5	5	Risk Char for CRA Grouping Stressors
Glenn E. Rice	NCEA	CIN	CRA/Risk Assessment	Co-author	10	5	
J. Michael Wright	NCEA	CIN	Epidemiology/CRA	Co-author	5	5	
Glenn E. Rice	NCEA	CIN	CRA/Risk Assessment	Co-author	5	10	
Beth Brewer	OSA	DC	CRA	Lead Author	15 ORISE	15 ORISE	DAG Paper
J. Michael Wright	NCEA	CIN	Epidemiology/CRA	Co-author	10	5	
Glenn Rice	NCEA	CIN	CRA/Risk Assessment	Co-author	10	5	
Lucas Neas*	NHEERL	RTP	Epidemiology	Co-author	NA	NA	
Deborah Segal	NCEA	DC	Toxicology/CRA	Co-author	5	10	Star Grant
Maggie Breville	NCER	DC	SHC/Grant Management	Lead author	NA	NA	Nonchem stressors
Total Subtask 6.2.1							
Maggie Breville*	NCER	DC	SHC/Grant Management	Lead Author	NA	NA	
Beth Brewer	OSA	DC	CRA		15 ORISE	15 ORISE	
Lucas Neas*	NHEERL	RTP	Epidemiology		NA	NA	
Glenn E. Rice	NCEA	CIN	CRA/Risk Assessment		25		
Deborah Segal	NCEA	DC	CRA/Toxicology	Co-author	5	10	
J. Michael Wright	NCEA	CIN	Epidemiology/CRA		20	15	
*Collaborator							

*Collaborator



Subtask 6.2.2 (RMS ID# HHRA 3.232.2): Cumulative Risk Assessment – Multiple Stressor Case Studies**Product 6.2.2.1. (RMS ID# HHRA 3.232.2.1) Resources:**

Extramural Resources: None

Lab or Center receiving money: NCEA

Division: CIN

Contact name: Glenn Rice

Extramural (NPD RAP) in \$K

- FY16: \$60K
- FY17: \$60K
- FY18: 0
- FY19: 0

Description of Extramural needs for each FY: Provided to ASPPH supporting Fellow's Salary and Benefits.

Description of impact on Product delivery (or contribution) if resources are not available in a timely manner: A delay might slow EPA's ability to efficiently characterize risks and benefits associated with green space from a cumulative risk perspective.

Proposed method for Extramural Need:

- Training Agreements: ASPPH
- Interagency Agreement:

Task Level Intramural Resources

Intramural (L/C Corporate) in \$K: N/A

Description of Intramural Needs for each FY: Salary Support

Special Task Level Resource Needs and Considerations

Special facilities or equipment needed: N/A

**Product 6.2.2.1. (RMS ID# HHRA 3.232.2.1) Staffing:**

Staff Member	L/C	Division	Expertise	Contribution to Product	FY16 % FTE	FY17 % FTE
Rebecca Gernes	ASPPH	CIN	CRA	Lead Author	20	20*
J. Michael Wright	NCEA	CIN	Epidemiology/CRA	Co-author	10	10
Glenn E. Rice	NCEA	CIN	CRA/Risk Assessment	Co-author	20	10

* While no longer an ASPPH Fellow, Rebecca Gernes will continue to work to complete the manuscript.

Product 6.2.2.2. (RMS ID# HHRA 3.232.2.2) Resources:Extramural Resources

Lab or Center receiving money: NCEA

Division: CIN

Contact name: Glenn Rice

Extramural (NPD RAP) in \$K

- FY16: \$20K
- FY17:
- FY18:
- FY19:

Description of Extramural needs for each FY: Funding for the ASPPH vehicle to compensate ASPPH Fellow.

Description of impact on Product delivery (or contribution) if resources are not available in a timely manner: A delay might slow EPA's ability to efficiently characterize the impact of greenspace exposure on risk of developing allergy from a cumulative risk perspective.

Proposed method for Extramural Need:

- Training Agreements: ASPPH
- Interagency Agreement

Task Level Intramural Resources

Intramural (L/C Corporate) in \$K: None



Description of Intramural Needs for each FY: None.

Special Task Level Resource Needs and Considerations

Special facilities or equipment needed: N/A

Product 6.2.2.2. (RMS ID# HHRA 3.232.2.2) Staffing:

Staff Member	L/C	Division	Expertise	Contribution to Product	FY16 % FTE	FY17 % FTE
Rebecca Gernes	ASPPH	CIN	CRA	author	50	-
J. Michael Wright	NCEA	CIN	Epidemiology/CR A	Co-author	10	-
Glenn E. Rice	NCEA	CIN	CRA/Risk Assessment	Co-author	15	-

Product 6.2.2.3 (RMS ID# HHRA 3.232.2.3):

Extramural Resources

Lab or Center receiving money: NCEA

Division: Washington

Contact name: Yu-Sheng Lin

Extramural (NPD RAP) in \$K

- FY16: None
- FY17: None
- FY18: None
- FY19: None

Description of Extramural needs for each FY: Literature search (e.g., extant ICF Inc.).

What science efforts are the funds needed for? Is there specific timing (i.e., contracts)?

See above for details. Contract timing: N/A

Description of impact on Product delivery (or contribution) if resources are not available in a timely manner? We do not anticipate any impact on product delivery.

Proposed method for Extramural Need: Contracts

Intramural Resources



Intramural (L/C Corporate) in \$K: TBD

Description of Intramural Needs for each FY: NA

Special Resource Needs and Considerations

Special facilities or equipment needed: N/A

Identify any of the following that apply: N/A

Product 6.2.2.3 (RMS ID# HHRA 3.232.2.3) Task Staffing

Staff Member	L/C	Division	Expertise	Contribution to Product	FY16 % FTE	FY17 % FTE	FY18 % FTE
Yu-Sheng Lin	NCEA	Washington	Biologist	Task Lead	-	10%	
Deborah Segal	NCEA	Washington	Neurotoxicity	Team member	-	5%	
Glenn Rice	NCEA	Cincinnati	Risk Assessment	Team member	-	5%	
Mike Wright	NCEA	Cincinnati	Epidemiologist	Team member	-	5%	

Product 6.2.2.4 (RMS ID# HHRA 3.232.2.4)



Subtask 6.2.2 (RMS ID# HHRA 3.232.2) Summary:

Subtask 6.2.2. (RMS ID# HHRA 3.232.2) Extramural Resources Summary

FY2016

	Product	Extramural Need or Activity	Amount Needed	New or Existing Vehicle
6.2.2.1.	GS Study	ASPPH salary	60K	Existing
6.2.2.2.	GS Workshop Report	ASPPH salary	20K	Existing
6.2.2.3.	CRA Kidney Disease	Contractor- literature search	0K	New
FY16 TOTAL				

FY 2017

	Product	Extramural Need or Activity	Amount Needed	New or Existing Vehicle
6.2.2.1.	GS Study	ASPPH salary	60K	Existing
6.2.2.2.				
6.2.2.3.				
FY17 TOTAL				

FY2018

	Product	Extramural Need or Activity	Amount Needed	New or Existing Vehicle
6.2.2.1.				
6.2.2.2.				
6.2.2.3.				
FY18 TOTAL				


Subtask 6.2.2. (RMS ID# HHRA 3.232.2) Staffing Summary

Staff Member	L/C	Div	Expertise	Contribution	FY16 % FTE	FY17 % FTE	FY18 % FTE	Product
Rebecca Gernes	ASPPH	CIN	CRA	Author	50 ASPPH	20* ASPPH	--	Green Space and Allergy
J. Michael Wright	NCEA	CIN	Epidemiology /CRA	Co-author	10	10	10	
Glenn E. Rice	NCEA	CIN	CRA/Risk Assessment	Co-author	20	10	10	
Rebecca Gernes	ASPPH	CIN	CRA	Author	50 ASPPH	--	--	Greenspace and CRA Workshop Report
J. Michael Wright	NCEA	CIN	Epidemiology /CRA	Co-author	10	--	--	
Glenn E. Rice	NCEA	CIN	CRA/Risk Assessment	Co-author	10	--	---	
Yu-Sheng Lin	NCEA	DC	Biologist	Lead Author		10	10	CRA Kidney Disease
Deborah Segal	NCEA	DC	Toxicology	Co-Author	-	5	5	
J. Michael Wright	NCEA	CIN	Epidemiology /CRA	Co-author	-	5	5	
Glenn Rice	NCEA	CIN	CRA/Risk Assessment	Co-author	-	5	5	
Total Subtask 6.2.2								
Yu-Sheng Lin	NCER	DC	Contract Management / Biologist			10	10-	
Rebecca Gernes	SPPH	CIN	CRA		50	20	--	
Glenn E. Rice	NCEA	CIN	CRA/Risk Assessment		30	15	10	
Deborah Segal	NCEA	DC	/Toxicology/CRA		5	5	5	
J. Michael Wright	NCEA	CIN	Epidemiology /CRA		20	15	10	

* While no longer an ASPPH Fellow, Rebecca Gernes will continue to work to complete the manuscript as time allows.



Task 6.3

(RMS ID# HHRA 3.233)

Applying Genetic and Epigenetic Data to Inform Susceptibility

Task Lead (TL): Susan Y. Euling (NCEA W)

Task Start Date: 06/01/2016

Task End Date: 09/30/2019

Task Description: The National Research Council's *Science and Decisions: Advancing Risk Assessment* (NRC, 2009) report stated that "Variability in human susceptibility has not received sufficient or consistent attention in many EPA health risk assessments..." Susceptibility is defined as *the capacity to be affected* (NRC, 2009). A person can be at greater or less risk relative to population median risk because of susceptibility factors including life stage, sex, genetics, socioeconomic status, prior exposure to environmental chemicals and/or pharmaceuticals, and stress. Greater knowledge of susceptibility in response to chemical and non-chemical stressors can be applied to EPA risk assessments.

Two important policy drivers that have required EPA to use susceptibility information in environmental chemical decision-making are the Food Quality Protection Act (FQPA, 1996) and the Safe Drinking Water Act amendments (SDWA, 1996). The FQPA (1996) mandated that EPA consider possible increased susceptibility of infants and children in the risk assessments of food-use pesticides; and the SDWA amendments (1996) required EPA to consider susceptible populations in risk assessments used in support of drinking water contaminant regulations. Approaches to address life-stage susceptibility in risk assessment have been described (e.g., EPA's Supplemental Guidance for Assessing Susceptibility for Early-Life Exposures to Carcinogens [EPA, 2005]). However, approaches to incorporate new, molecular types of information to inform susceptibility are needed. The goal of Task 6.3 is to apply emerging molecular data to inform susceptibility for risk assessment.

Epigenetic, genomic, DNA sequencing, and polymorphism data are molecular data types that can be used to inform susceptibility and variability. These data have the potential to define susceptible populations and in turn, increase our knowledge of variability in response to a chemical exposure. The application of the knowledge gained from these molecular data types can enhance our community, single chemical and cumulative risk assessments. EPA, faced with the challenge of evaluating and integrating these new data types in risk assessment, can borrow approaches (e.g., Adverse Outcome Pathway [AOP] Framework [Ankley et al., 2010]) for integrating the data at different levels of biological organization, for adverse outcomes, into risk assessment. In addition to the need for data evaluation and integration, EPA also needs to



understand the study design requirements in order to identify transgenerational effects, which could be mediated by an epigenetic mechanism, in chemical testing. Task 6.3. (*RMS ID# HHRA 3.233*) products have developed innovative science to use molecular data streams and newer analysis approaches to inform susceptibility.

Task 6.3 is separated into two subtasks, one utilizing epigenetic data (i.e., DNA methylation, microRNA expression, and histone modification) and one utilizing genetic susceptibility data (i.e., polymorphism, microarray, DNA sequence) to inform community risk assessment. Task 6.3. (*RMS ID# HHRA 3.233*) intersects with and may inform other HHRA efforts to develop approaches for using new, molecular data types, e.g., epigenetics; HHRA Project 8 (*RMS ID# HHRA 4.22*, “Applying Emerging Science to Inform Risk Screening and Assessment”, especially Task 8.1. (*RMS ID# HHRA 4.221*, “Disease-based Integration of New Data Types”). Subtask 6.3.1. is informed by an HHRA workshop on epigenetics and cumulative risk ([[HYPERLINK "https://remoteworkplacedr.epa.gov/ncea/risk/DanaInfo=.acgrxfEkwilqz7+recordisplay.cfm?deid=308271" \o "Cmd+Click or tap to follow the link" \]](https://remoteworkplacedr.epa.gov/ncea/risk/DanaInfo=.acgrxfEkwilqz7+recordisplay.cfm?deid=308271)) held in August 2015. Workshops are conducted on critical challenges as part of Task 7.5 (*RMS ID# HHRA 4.215*). The output of the task will support the EPA programs (OW, Children’s Office) and regions as well as risk assessors inside and outside of the Agency.

- **Subtask 6.3.1. (*RMS ID# HHRA 3.233.1*): Applying Epigenetics Data to Cumulative Risk**

Twin studies have shown that expression of diseases is not completely concordant between monozygotic twins and thus, arise in part from differences in environmental factors. Epidemiological and laboratory studies suggest that some environmental chemicals as well as some nonchemical stressors are capable of affecting human health through a variety of epigenetic mechanisms. Epigenetics is defined as heritable phenotypic traits due to chromatin changes without DNA sequence changes. Epigenetic changes include DNA methylation (hypo or hypermethylation), histone modifications (e.g., acetylation, methylation, glycosylation) and microRNA expression (down or up regulations of specific microRNAs). Evidence suggests that various stressors can influence disease outcomes through the accumulation of epigenetic modifications. There is a need to understand the complex interactions among epigenetics, the environment, and disease.

Data on epigenetics are not routinely evaluated in risk assessment because of either a lack of data or a lack of expertise in evaluating these data. To address the need for approaches to evaluate these data, subtask 6.3.1. products of literature reviews, case studies, and workshop findings, will increase our ability to interpret these data for cumulative risk assessment.

Science questions that are addressed in Subtask 6.3.1. include the following:



- What are the issues regarding interpretation of epigenetic data (for each of the different markers) and transgenerational effects data for risk assessment? (Products 6.3.1.1, 6.3.1.2, 6.3.1.3, and 6.3.1.5)
- Are there approaches to evaluate the quality of publicly available epigenetic data? (Product 6.3.1.1, and 6.3.1.5)
- Are there approaches for determining whether there is a causal relationship between an identified epigenetic marker and a disease outcome? (Products 6.3.1.1 – 6.3.1.5)
- How can nonchemical stressors, which may modulate epigenetic effects after exposure to environmental chemicals, be considered in risk assessment? (Products 6.3.1.1, 6.3.1.2, 6.3.1.3, and 6.3.1.5)
- What is the adequacy of current chemical test methods to identify transgenerational effects? (Product 6.3.1.4)
- What evidence is necessary to support the conclusion that an epigenetic mechanism of action underlies transgenerational effects? (Product 6.3.1.4)

The impact of the work performed in Subtask 6.3.1 (*RMS ID# HHRA 3.233*) will be increased knowledge, experience, and expertise in evaluating, interpreting, and integrating epigenetic data and transgenerational effect data in EPA risk assessment, particularly with respect to interindividual variability and susceptibility to environmental chemicals.

- **Subtask 6.3.2. (*RMS ID# HHRA 3.233.2*): Applying Polymorphism and Mechanistic Data to Inform Genetic Susceptibility**

- ✓ Defining genetic susceptibility, or inter-individual genetic variation, that impacts response to environmental chemicals across human populations is an area of interest to EPA regions and programs that must evaluate susceptibility for their community and for chemical risk assessment. Molecular data streams including polymorphism data, DNA sequencing data, and genomic data can inform intraspecies variability, due to genetics, in response to chemical exposure. Lessons learned from the 6.3.2. products will improve EPA's expertise in evaluating, interpreting and integrating genetic susceptibility data in risk assessment and will aid the development of enhanced approaches for defining genetic variability/susceptibility to chemical exposures.

Science questions that are addressed in Subtask 6.3.2. (*RMS ID# HHRA 3.233.2*) include the following:

- Can an approach be developed for utilizing polymorphism, genomics, and other mechanistic data to inform susceptibility for risk assessment (at the community, single and multi-chemical level)? Can the AOP Framework



- enhance our ability to integrate these different data types? (Products 6.3.2.1 and 6.3.2.2)
- What are the issues regarding interpretation of polymorphism data, DNA sequence, and mechanistic data for informing genetic susceptibility that impacts human response to environmental chemical exposures? Are there publicly available data sources that EPA can utilize? (Products 6.3.2.1 and 6.3.2.2)
- Are there approaches for evaluating the quality of publicly available polymorphism, DNA sequence, and genomic data? (Product 6.3.2.1)

The impact of the work performed in Task 6.3. (*RMS ID# HHRA 3.233*) will be the establishment of EPA expertise in evaluating, interpreting, and integrating genetic and epigenetic data for the purpose of improving our understanding of susceptibility information in risk assessment. The products within Task 6.3. (*RMS ID# HHRA 3.233*) are designed to support risk assessments within EPA, the Programs, Regions and EPA's Children's Office, and outside of EPA. Utilizing molecular data to gain knowledge about susceptibility may also inform community decision-making including environmental justice (EJ) issues. ~~one of the EPA Administrator's themes, Making a Visible Difference in Communities across the Country.~~

Task Approach:

In addition to the subtask descriptions (above), further details regarding the approaches taken in each of the two subtask areas, the first aimed at the use of epigenetic information and the second aimed at genetic data to inform susceptibility considerations, can be found in the product descriptions for each subtask that follow.

Task Products:

- **Subtask 6.3.1. (*RMS ID# HHRA 3.233.1*): Applying Epigenetics Data to Cumulative Risk**
- **Product 6.3.1.1. (*RMS ID# HHRA 3.233.1.1*)**
- **Product's Delivery Date:** 9/30/16 (Submission to journal)
- **Product's Contribution to Output:** This workshop report will contribute to the overall understanding of how to utilize epigenetics information in cumulative risk and community-based risk assessment.
- **Product Type:** Workshop report in the form of a manuscript submitted to a peer-reviewed journal.
- **Product's Timeline (with milestones):** Workshop held, Sept 2-3 2015; Journal submission of manuscript reporting on workshop 9/30/2016.
- **Product's intended user/customer/audience:** Risk assessment community; EPA programs addressing chemical contamination, environmental justice and childrens' health.
- **Is this a key product?** YES.



- **Related products:** This would coordinate with the efforts in other tasks related to epigenetics (in this Subtask 6.3.1.) as well as a recently convened workshop in Task 7.5. (HHRA Workshop held September 2-3, 2015; Available online at: [[HYPERLINK "https://remoteworkplacedr.epa.gov/ncea/risk/,DanaInfo=.acgrxfEkwiIqz7+recordisplay.cfm?deid=308271"](https://remoteworkplacedr.epa.gov/ncea/risk/,DanaInfo=.acgrxfEkwiIqz7+recordisplay.cfm?deid=308271) \o "Cmd+Click or tap to follow the link"])
- **Product 6.3.1.2. (RMS ID# HHRA 3.233.1.2)**
- **Product Title: Nonchemical Stressors, Epigenetic Changes, Susceptibility to Air Pollution Exposure, and Cardiovascular Disease**
- **Product Contact (email):** Bob Devlin (devlin.robert@epa.gov)
- **Product's Delivery Date:** 9/30/18
- **Product Description:** The collaboration between the National Health and Environmental Effects Research Laboratory (NHEERL) with Duke University on a clinical study of CATHeterization patients for GENetic determinants of coronary artery disease (CATHGEN) is a human population study in North Carolina. HHRA, via integration and collaboration with the SHC and ACE research programs, is interested in utilizing this population to study human epigenetic changes that lead to disease susceptibility. The specific HHRA hypothesis that will be tested is: Alterations in the epigenome arise from nonchemical stressors, specifically from adverse socio-economic circumstances (SEC) encountered through residence in disadvantaged neighborhoods. These stable alterations of the epigenome lead to changes in expression of genes critical for human health as well as pathways that alter human susceptibility to environmental toxicants.

The association between air pollution and increased adverse cardiovascular outcomes has been well-established. However, societal factors that can modify an individual's outcome have not been well characterized. SECs are well-established determinants of health status and are associated with decreased life span and increased disease. Areas with poor SEC such as poverty, exposure to crime, unemployment, limited access to fresh foods, etc., are characteristics of disadvantaged neighborhoods. This product addresses the following specific hypothesis: do individuals who live in disadvantaged neighborhoods have alterations in the epigenome that differ from those who live in advantaged neighborhoods and, if so, can specific biological pathways controlled by those epigenetic changes be linked with susceptibility to air pollution? To address this problem, disadvantaged and advantaged neighborhoods in Wake and Durham counties will be characterized and construct a neighborhood deprivation index based on multiple criteria including poverty, education, unemployment, exposure to crime, exposure to pollution, and access to amenities. We will compare the epigenetic profile (specifically, the DNA methylation status) of individuals within and across neighborhoods to determine if residence in a specific neighborhood is associated with an epigenetic profile (i.e., differential changes in the epigenome associated with specific cellular pathways such as stress pathways). We will identify global or pathway-specific



epigenetic changes associated with residence in disadvantaged neighborhoods (compared with other types of neighborhoods), where people are more likely to have cardiovascular disease and may also be more susceptible to air pollutants.

- **Product Type:** A draft manuscript will be prepared for publication in a peer-reviewed journal.
 - **Product's Contribution to Output:** This study will focus on identifying stable epigenetic changes as a mechanism by which people are more susceptible to environmental pollutants.
 - **Product's Timeline (with milestones):**
 - a. DNA methylation data analysis complete: 4/30/17
 - b. Draft manuscript out for review to team and HHRA: 6/30/17
 - c. Review of manuscript; Additional analyses completed: 12/30/17
 - d. Revisions made to manuscript: 4/30/18
 - e. Manuscript submitted to NCEA clearance: 7/30/18
 - **Product's intended user/customer/audience:** OAR places a high priority on identification of susceptible populations. This study will also provide NCEA with mechanistic information that will be useful in performing risk assessments of individuals residing in disadvantaged communities.
 - **Is this a key product?** No.
 - **Does this Product contribute to a Product under another Task? If so, identify other Task.** Yes, this product is related to Product 6.3.1.3. (below) in this subtask. The larger CATHGEN study is a collaboration between SHC, ACE and HHRA ORD research programs to fully explore SES factors associated with living in disadvantaged neighborhoods that determine environmental health.
-
- **Product 6.3.1.3. (RMS ID# HHRA 3.233.1.3)**
 - **Product Title: Epigenetic Alterations: A Mechanism Through Which Nonchemical Stressors Increase Susceptibility to Chemical Stressors**
 - **Product Contact (email):** Deborah Segal (segal.deborah@epa.gov)
 - **Product's Delivery Date:** 9/30/19
 - **Product Description:** Research has demonstrated that psychosocial stress, a nonchemical stressor, results in epigenetic changes. Many of these epigenetic changes affect the functioning of the Hypothalamic-Pituitary-Adrenal axis. For this product, we will investigate whether such epigenetic changes resulting from psychosocial stress can help to explain the interaction of psychosocial stress with chemical stressors, such that individuals who are exposed to higher levels of psychosocial stress may face greater developmental neurotoxicity following exposure to toxic chemicals. As low-socioeconomic status (SES) communities are believed to confront higher levels of psychosocial stress and chemical exposures than higher SES communities, this research



will have important implications for community-based risk assessments in lower-income and environmental justice communities.

- **Product Type:** Submission of a Manuscript to a peer-reviewed journal.
- **Product's Contribution to Output:** This case study will help to elucidate one mechanism by which nonchemical stressors exacerbate the response to chemical exposures. The results of the case study will have broad application to understanding potential interactions between nonchemical stressors and responses to chemical exposures, which could in turn lead to improved community health protection.
- **Product's Timeline (with milestones):**
 - Final Draft Journal Manuscript to Coauthors: 3/30/19
 - Journal Manuscript Internal Review and EPA Clearance: 5/1/19
 - Journal Manuscript Submission: 9/30/19
- **Product's intended user/customer/audience:** Risk assessors in EPA Regions and Program Offices (accessible to scientists and managers). This product will build on efforts underway in Task 6.2 to understand interactions of chemical/nonchemical stressors. Further, this product may help to develop future methods for considering chemical/non-chemical stressor interactions in risk assessments.
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task?** No.

- **Product 6.3.1.4. (RMS ID# HHRA 3.233.1.4)**
- **Product Title:** Incorporating Transgenerational Testing and Epigenetic Mechanisms into Chemical Testing and Risk Assessment: A Literature Survey of Transgenerational Responses in Environmental Chemical Studies
- **Product Contact (email):** Susan Makris ([HYPERLINK "mailto:makris.susan@epa.gov"])
- **Product's Delivery Date:** 12/30/17
- **Product Description:** A number of environmental chemicals have been shown to alter epigenetic markers. Some published multi-generation rodent studies have identified effects on F2 and later generations after chemical exposures solely to F0 dams, but these studies were not focused on chemical safety. A question of interest is - What is the adequacy of current test methods to identify transgenerational effects? To address the specific question of how could outcomes related to epigenetic changes be identified and incorporated into chemical testing and risk assessment, a systematic literature review will be conducted to identify transgenerational studies in rodents. The studies will be evaluated to characterize the methods and observed outcomes, and to identify strengths, limitations, and biases.

A preliminary evaluation of a subset of the literature found that many of the studies identify chemicals or combinations of chemicals that produce transgenerational effects and/or adult-onset diseases, but there appears to be a paucity of published studies indicating a lack of transgenerational effects, perhaps due to publication bias. A number



of study design issues were identified including the numbers of litters assigned to control and test groups are not always transparently reported, nested statistical analyses of data are not always utilized to address litter effects, and “blind” testing is seldom performed.

- **Product Type:** Submission of a Manuscript to a peer-reviewed journal.
 - **Product’s Contribution to Output:** This effort will be focused on identifying ways in which potential hazards identified in transgenerational epigenetic research studies might be applied to the traditional toxicity testing and risk assessment paradigm for environmental chemicals.
 - **Product’s Timeline (with milestones):**
 - March 2016 - HERO literature search
 - April 2016 - Identify and download pdfs for transgenerational epigenetic studies
 - June 2016 - Evaluate studies
 - August 2016 - Analyze results
 - November 2016 - Draft manuscript
 - Jan 2017 – Team review
 - March 2017 – Literature search update; evaluation of epigenetic data
 - June 2017 – Revise and perform scientific peer review
 - September 2017 - Initiate EPA review and clearance process
 - December 2017 - Submit manuscript for publication
 - **Product’s intended user/customer/audience:** There is interest in this topic in the broad scientific and risk assessment community. The manuscript will address the evaluation and use of transgenerational studies for risk evaluation in ORD/NCEA (IRIS assessments), Program Offices such as OSCPP, OW, OSWER, and OCHP, and Regional Offices. In addition, it will provide information useful to EPA research laboratories (e.g., NHEERL) as they design studies to study transgenerational epigenetic effects.
 - **Is this a key product?** No.
 - **Does this Product contribute to a Product under another Task?** If so, identify other Task. This product will support assessments in the HHRA program.
-
- **Product 6.3.1.5. (RMS ID# HHRA 3.233.1.5)**
 - **Product Title:** Interpreting Epigenetic Data for Risk Assessment: A Framework
 - **Product Contact (email):** Susan Euling (euling.susan@epa.gov)
 - **Product’s Delivery Date:** September 2019
 - **Product Description:** EPA needs to determine the appropriate methods for and issues in epigenetic data interpretation for single and multiple chemical risk assessment. A framework for risk assessors to structure their literature and data identification, review, study quality evaluation, and interpretation of epigenetic data for risk assessment is needed. Components of the report will include lessons learned/recommendations from the completion of Products 1-4 regarding: 1) Data quality assessment; 2) epigenetic data



sources; 3) evaluation of causality between the various epigenetic markers and later life disease; 4) approaches for epigenetic data analysis.

- **Product Contributors:** Anu Mudipalli (NCEA W); Janice Lee, (NCEA IRIS); Susan Makris, (NCEA W); Deb Segal (NCEA W).
- **Product Type:** Submission of Journal Article to peer-reviewed journal.
- **Product's Contribution to Output:** A framework that provides risk assessors with a method to structure their literature searches, review, quality assessment, and interpretation of epigenetic data for risk assessment. This is one of the key outputs of Subtask 6.3.1.
- **Product's Timeline (with milestones):**
 - December 2015 - Initiate HERO literature search; identify publicly available human epigenetic data sources
 - August 2016 – Evaluate studies: Identify study quality issues
 - December 2016 - Evaluate epigenetic data sources: Identify study quality issues
 - August 2017 – Expert review of data: causal relationship issue
 - December 2018 – Compile lessons learned from Products 1-4
 - August 2018 - Draft manuscript
 - October 2018 – Revisions based on team review
 - February 2019 – Incorporate newly completed Task 6.3.1. product findings into the framework
 - March 2019 - Initiate EPA review and clearance process
 - September 2019 – Submit manuscript to journal
- **Product's intended user/customer/audience:** There is interest in evaluating epigenetic data in the broad scientific and risk assessment community. The manuscript will address the evaluation and use of epigenetics data for risk evaluation in ORD/NCEA (IRIS assessments), Program Offices such as OSCPP, OW, OSWER, and OCHP, and Regional Offices.
- **Is this a key product?** TBD.
- **Does this Product contribute to a Product under another Task?** If so, identify other Task. No



Subtask 6.3.2. (RMS ID# HHRA 3.233.2): Applying Polymorphism and Mechanistic Data to Inform Genetic Susceptibility in Risk Assessment

Product 6.3.2.1. (RMS ID# HHRA 3.233.2.1)

- **Product Title:** Evaluation of Approaches to Incorporate Novel Human Genetic Susceptibility Information in Risk Assessment (review article).
- **Product contact (email):** Susan Euling, NCEA-W (euling.susan@epa.gov); Contributors: Holly Mortensen, NHEERL; Bonnie Joubert, NIEHS; Janice Lee, IRIS; Nisha Sipes, NIEHS.
- **Product's Delivery Date:** 9/30/17
- **Product Description:** In human health risk assessment, data on susceptibility can be derived based on available data on susceptible populations or, in the absence of susceptibility data, an intraspecies uncertainty factor may be applied to account for the lack of information. Defining genetic susceptibility in response to environmental chemicals across human populations is an area of interest in the NAS' new paradigm of toxicity pathway-based risk assessment (NRC, 2010; Krewski et al., 2014). This project will explore the utility of new data streams to inform genetic susceptibility to adverse outcomes for application to community and cumulative risk assessment. One approach for integrating mechanistic and polymorphism data in order to characterize genetic susceptibility to chemical exposure has been described by Mortensen and Euling (2013). Since the time of the publication, additional data sources are now available that can be used to explore genetic susceptibility and mechanisms of action. Additionally, integrative approaches including the chemical-agnostic AOP framework (Ankley et al., 2010) may be useful constructs for organizing these data types particularly for cumulative risk assessment purposes. The manuscript will review the available approaches, publically available data sources, and make recommendations for the incorporation of human genetic susceptibility information for risk assessment.
- **Product Type:** Submission of manuscript to peer-review journal.
- **Product's Contribution to Output:** The manuscript will provide a critical review the data sources and approaches for incorporating human genetic inter-individual variability information in risk assessment.
- **Product's Timeline (with milestones):**
 - May 2016: Initiate literature search
 - July 2016: Begin search for data sources
 - September 2016: Begin drafting manuscript
 - November 2016: Team review and revisions
 - February 2017: Internal Review of manuscript and revisions
 - May 2017: Clearance process begun
 - September 2017: Submission to peer-reviewed journal
- **Product's intended user/customer/audience:** Risk assessors in EPA's Regional and Program Offices. In particular, Region 3 is interested in this approach and case study in risk assessment for environmental chemicals (Gross-Davis et al., 2015). This product will



build capacity in utilizing publically available polymorphism, genomic, and sequencing data in risk assessment, making it useful to new chemical assessments at EPA.

- **Is this a key product?** Yes.
- **Does this Product contribute to a Product under another Task? If so, identify other Task.** Yes. HHRA 6.1. (*RMS ID# 3.231*) is considering the AOP framework for the integration of ecological and human data so this product will contribute to that task. A related manuscript has been proposed as a Milestone for CSS Task 1.1c: Taxonomic Relevance of AOPs, for specifically between species relevance of AOPs.
- **Subtask 6.3.2. (*RMS ID# HHRA 3.233.2*): Applying Polymorphism and Mechanistic Data to Inform Genetic Susceptibility in Risk Assessment at the Population Level**
- **Product 6.3.2.2 (*RMS ID# HHRA 3.233.2.2*). Incorporation of Intraspecies Genetic Susceptibility Information: Case Study Using AOP Approach**
- **Product contact (email):** Holly Mortensen, NHEERL (mortensen.holly@epa.gov); Contributors: Janice Lee, (NCEA IRIS); Susan Euling (NCEA W).
- **Product's Delivery Date:** 3/30/19
- **Product Description:** This product is a collaboration among EPA NHEERL, EPA NCEA, and NIEHS.
- Utilizing the findings and recommendations from the review article (above) in Product 6.3.2.1 (*RMS ID# HHRA 2.233.1*), one case study based on an AOP will be developed using the available data. The case study will make use of gene targets, including environmentally sensitive genes (ESGs), that have been identified and characterized across human populations. . ESG data have been useful in determining genetic susceptibility to a health outcome in a community (Gross-Davis et al., 2015). The case study will allow us to examine the utility of publically available human genomic, transcriptomic, and phenotypic data sources for evaluating between individual and population level variation at loci associated with an adverse outcome. The relevance of genetic differences at ESGs between individuals, and the consequence for variation in phenotypes relevant to an adverse outcome at the population level, will be explored. In addition, issues and research needs in utilizing these data will be identified.
- **Product Type:** Submission of manuscript to peer-review journal
- **Product's Contribution to Output:** This manuscript will test an approach for the implementation of human genetic data to inform genetic susceptibility in risk assessment.
- **Product's Timeline (with milestones):**
 - February 2017: Based on review manuscript findings, design case study selection process.
 - April 2017: Discussions with HHRA regarding selecting the case study.
 - June 2017: Final selection of case study and initiate compiling available data sources
 - September 2017: Begin consolidation of data sources and analyses



- January 2018: Begin drafting manuscript
- March 2018: Additional data analyses (if needed)
- September 2018: Team review and revisions
- December 2018: Revisions completed; Any additional work needed
- January 2019: Clearance initiated
- March 30, 2019: Submission to peer reviewed journal
- **Product's intended user/customer/audience:** Risk assessors in EPA Regions and Program Offices. In particular, Region 3 is interested in this approach and case study in risk assessment for environmental chemicals (Gross-Davis et al., 2015). This product will build capacity in utilizing publically available polymorphism, genomic, and DNA sequencing data in risk assessment.
- **Is this a key product?** No.
- **Does this Product contribute to a Product under another Task? If so, identify other Task.** Yes, Task 6.1.

Overall Task Constraints:

Define scientific, logistical, and technical constraints associated with completing the Task

- ✓ **Scientific:** Janice Lee, Raghu Nath, Deb Segal, Anu Mudipalli, Nagu Keshava, Yu-Sheng Lin, Susan Euling, Susan Makris, and Teneille Walker work on IRIS chemicals. They may have a change in their availability due to high priority chemical assignments. Holly Mortensen works at NHEERL's genomics core and thus, has incoming work requests that may be of higher priority. Bonnie Joubert and Nisha Sipes work at NIEHS and have other commitments.
- ✓ **Logistical:** There may be a lag in the time to award of a contract and work order on an existing contract.
- ✓ **Technical:** Need for specific data and analyses (products 6.3.1.2, 6.3.1.3, and 6.3.2.2).
- ✓ **Resources:** Time to award of contracts and hiring are potential constraints.

Task Dependencies:

- ✓ **Dependency:** Product 6.3.1.5 is dependent on the completion of products 6.3.1.1-4. Product 6.3.2.2 is dependent on the completion of product 6.3.2.1.

Task Resources: *Please see funding and FTE tables, below.*

References

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Mortensen H and Euling SY, 2013. Integrating mechanistic and polymorphism data to characterize human genetic susceptibility for environmental chemical risk assessment in the 21st century. *Toxicol Appl Pharmacol*. 271(3):395-404.

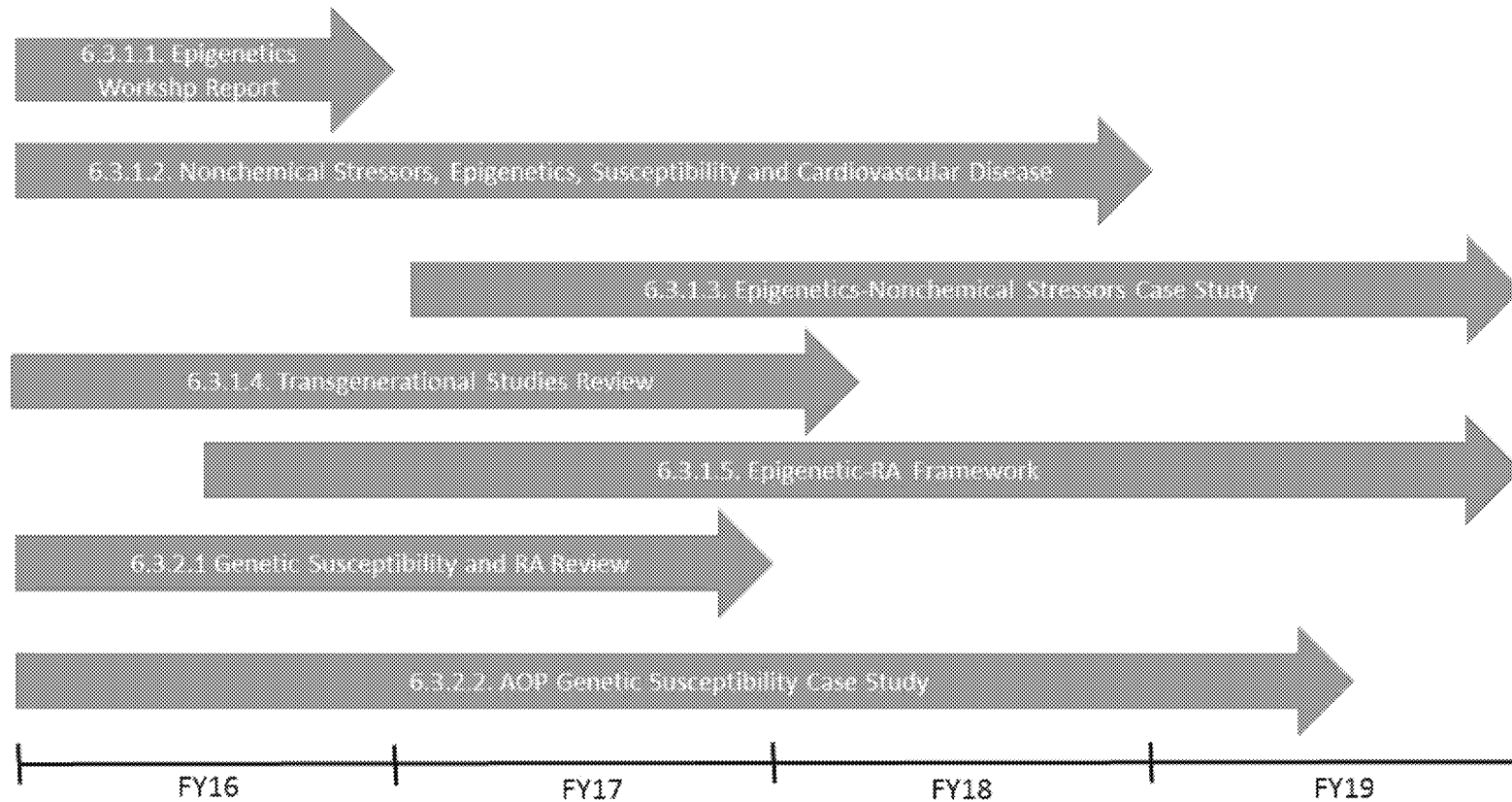
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Task 6.3. Figure 6-2. Timeline by Product



**Task 6.3. Resources by Subtask****Subtask 6.3.1.:**

Product	Lead Scientist	Div	Extramural Resources \$K				Intramural Resources \$K			
			FY16	FY17	FY18	FY19	FY16	FY17	FY18	FY19
Epigenetics Workshop Report	White & Walker	DC	0	10	0	0	0	0	0	0
Nonchem stress, epigenetics, susceptibility to air pollution, and CVD	Devlin	NHEERL-RTP	100	0	0	0	0	0	0	0
Epigenetics/ Nonchem Stress Case Study	Segal	DC	0	27.5	10	10	0	0	0	0
Transgen Studies Review	Makris	DC	0	37.5	0	0	0	0	0	0
Epigenetics Framework	Euling	DC	0	47.5	40	40	0	0	0	0
Total			100	115.5	50	50	0	0	0	0

**Subtask 6.3.2.:**

Product	Lead Scientist	Div	Extramural Resources \$K				Intramural Resources \$K			
			FY16	FY17	FY18	FY19	FY16	FY17	FY18	FY19
Genetic Susc Review	Euling	W	0	22.5	10	0	0	0	0	0
Genetic Susc Case Studies	Mortensen	NHEERL ISTD	45	50	60	0	0	0	0	0
Total			45	72.5	70	0	0	0	0	0

*Collaborator

Task 6.3. Funding by Fiscal Year**FY16**

Product	Funding Source	Funding Amount	New or Existing
6.3.1.2 Nonchem stressors/epigenetics/CVD	Contract	\$100,000	Existing
6.3.2.2. Genetic Susceptibility Case Studies	Student Services contractor (gathering data sources; testing computational tools)	\$45,000 (100%; full-time)*	New

*assuming full-time student services contractor is approx \$45,000/yr

**FY17**

Product	Funding Source	Funding Amount	New or Existing
6.3.1.1. Epigenetics Workshop Report (ms)	Journal page charges (PO)	\$10,000	New
6.3.1.3. Epigenetics Nonchem Stressors Case Study	Student Services contractor (lit searches, article review; data entry)	\$27,500 (half-time)*	New
6.3.1.4. Transgen Study Review	Student Services contractor (article review; data entry)	\$27,500 (half time)*	New
	Page charges via Purchase Order	\$10,000	New
6.3.1.5. Evaluating epigenetics data	Student Services contractor (data entry; identification of data sources; drafting article)	\$27,500 (half time)*	New
	ICF Contract: Editing, Tables, Figures	\$20,000	Existing
6.3.2.1. Genetic susceptibility Review	Student Services contractor (testing computational tools)	\$22,500 (50% of full-time)*	New
6.3.2.2. Genetic Susceptibility Case Studies	ORISE Postdoc (expertise in bioinformatics)	\$50,000 (50% of full-time)**	New

*assuming full-time student services contractor is approximately \$55,000/yr for DC area; \$45,000 for RTP area; **assuming full-time for ORISE post-graduate fellow or post-doctoral fellow is approximately \$100,000/yr

FY18

Product	Funding Source	Funding Amount	New or Existing
6.3.1.3. Epigenetics Nonchem Stressors Case Study	Reviewing, QA/QC support (ICF or SRC)	\$10,000	Existing
6.3.1.5. Evaluating epigenetics data	ICF Contract: Writing, Editing, Tables, Figures	\$40,000	Existing
6.3.2.1. Genetic susceptibility Review	Page charges via Purchase Order	\$10,000	New
6.3.2.2. Genetic Susceptibility Case Study	Postdoc (bioinformatics)	\$50,000 (50% of full-time)*	New
	Page charges via Purchase Order	\$10,000	New

*assuming full-time for ORISE post-graduate fellow or post-doctoral fellow is approximately 100,000/yr

FY19

Product	Funding Source	Funding Amount	New or Existing
6.3.1.3. Epigenetics Nonchem Stressors Case Study	Page charges via Purchase Order	\$10,000	New
6.3.1.5. Evaluating epigenetics data	ICF Contract: Writing, Editing, Tables, Figures	\$40,000	Existing

*assuming full-time for ORISE post-graduate fellow or post-doctoral fellow is approximately \$100,000/yr

**Task Staffing:**

Staff Member	L/C	Div	Expertise	Contribution to Task, Product name (number)	FY16 %FTE	FY17 %FTE	FY18 %FTE	FY19 %FTE
Paul White	ORD/NCE A	W	Risk Assessment; Modeling	Co-Lead: Epigenetics Workshop Report (6.3.1.1.)	20	10		
Teneille Walker	NCEA	IRIS	Risk Assessment/ Toxicology	Co-Lead: Epigenetics Workshop Report	20	10		
Kenneth Olden	NCEA	IO	Center Director; Environmental Health	Co-Lead: Epigenetics Workshop Report	NA	NA		
Robert Devlin	ORD/ NHEERL	EPH	Developmental biology	Lead: Nonchem stressors/ epigenetics/susceptibility/CVD (6.3.1.2.)	25	0	0	0
Yu-Sheng Lin	NCEA	W	Exposure biomarkers	Team member: Epigenetic-disease case studies	5	5	5	5
Janice Lee	IRIS	RTP	Toxicology and Risk Assessment	Team member: Epigenetic-disease case studies	5	5	5	5
Nagu Keshava	NCEA	W	Toxicology	Team member: Epigenetic-disease case studies	5	5	5	5
ORISE Postdoc	NCEA	W	Epigenetics	Team member: Epigenetic-disease case studies	0	50	50	50
Anu Mudipalli	NCEA	W	Toxicology	Team member: Epigenetic-disease case studies	5	5	5	5
Deb Segal	NCEA	W	Cumulative Risk Assessment/ Toxicology	Lead: Epigenetic Nonchemical Stressors (6.3.1.3.)		5	10	10
Susan Euling	NCEA	W	Dev and Repro Biology/Genetics	Co-Author: Epigenetic Nonchemical Stressors		5	5	5



Staff Member	L/C	Div	Expertise	Contribution to Task, Product name (number)	FY16 %FTE	FY17 %FTE	FY18 %FTE	FY19 %FTE
Susan Makris	NCEA	W	Developmental and Repro Tox	Lead: Transgen Epigenetics Review (6.3.1.4.)	20	10	10	
Susan Euling	NCEA	W	Developmental and Repro Tox and Genetics	Co-Author: Transgen Epigenetics Review	5	5	5	
Teneille Walker	NCEA	IRIS	Risk Assessment/ Toxicology	Co-Author: Transgen Epigenetics Review	5	5	5	
Susan Euling	NCEA	W	Dev and Repro Biology/Genetics	Lead: Epigenetic data interpretation framework (6.3.1.5.)	5	5	10	10
Deb Segal	NCEA	W	Cumulative Risk Assessment/ Toxicology	Co-Author: Epigenetic data interpretation framework	5	5	5	5
Anu Mudipalli	NCEA	W	Toxicology	Co-Author: Epigenetic data interpretation framework	3	5	5	5
Susan Makris	NCEA	W	Developmental and Repro Tox	Co-Author: Epigenetic data interpretation framework	5	5	5	5
Janice Lee	IRIS	RTP	Toxicology and Risk Assessment	Co-Author: Epigenetic data interpretation framework	3	5	5	5
Susan Euling	NCEA	W	Dev and Repro Biology/Genetics	Lead: Genetic susceptibility approach w/AOP framework - review (6.3.2.1.)	10	20		
Holly Mortensen*	NHEERL	RTP	Genetics/ Bioinformatics	Co-Author: Genetic susceptibility approach w/AOP framework - review	NA	NA		



Staff Member	L/C	Div	Expertise	Contribution to Task, Product name (number)	FY16 %FTE	FY17 %FTE	FY18 %FTE	FY19 %FTE
Bonnie Joubert*	NIEHS	RTP	Genetics	Co-Author: Genetic susceptibility approach w/AOP framework - review	NA	NA		
Nisha Sipes*	NIEHS	RTP	Genetics	Co-Author: Genetic susceptibility approach w/AOP framework - review	NA	NA		
Janice Lee	IRIS	RTP	Toxicology and Risk Assessment	Co-Author: Genetic susceptibility approach w/AOP framework - review	10	10		
Student services contractor	NCEA	RTP or W	Toxicology or biology	Co-Author: Genetic susceptibility approach w/AOP framework - review	50	50		
Holly Mortensen*	NHEERL	RTP	Genetics/ Bioinformatics	Lead: Genetic susceptibility w/AOP Case Study (6.3.2.2.)	NA	NA	NA	NA
Susan Euling	NCEA	W	Dev and Repro Biology/Genetics	Co-Author: Genetic susceptibility w/AOP Case Study	5	5	5	5
Janice Lee	IRIS	RTP	Toxicology and Risk Assessment	Co-Author: Genetic susceptibility w/AOP Case Study	5	5	5	5
Postdoc	NCEA	RTP or W	Toxicology or biology	Co-Author: Genetic susceptibility w/AOP Case Study	50	50	50	50



Staff Member	L/C	Div	Expertise	Contribution to Task, Product name (number)	FY16 %FTE	FY17 %FTE	FY18 %FTE	FY19 %FTE
Nisha Sipes*	NIEHS	RTP	Biological modeling	Co-Author: Genetic susceptibility w/AOP Case Study	NA	NA	NA	NA
Bonnie Joubert*	NIEHS	RTP	Genetics	Co-Author: Genetic susceptibility w/AOP Case Study	NA	NA	NA	NA

*Collaborators outside of NCEA; FTE not accounted.



Task 6.4
(RMS ID# HHRA 3.234)
Apportioning Multimedia Exposure and Risk
Across Human and Ecological Receptors

Task Lead (TL): Jennifer Richmond-Bryant (NCEA RTP)

Task Start Date: 10/01/2015

Task End Date: 09/30/2019

Task Description:

The National Academy of Sciences stated that to address community concerns about exposure to stressors, “as the number and types of stressors and endpoints under consideration increase, decisions must be made about which dimensions should be considered as components of risk assessment as defined and used by EPA.” (National Research Council, 2008). This Task will focus on relationships among multiple stressors and their sources to human and ecologic receptors for the purpose of apportioning risk. Hence, the overall objectives of this task are 1) to address scientific challenges regarding integration of exposure assessment considerations for multiple stressors into cumulative risk applications and 2) to explore stressors that may modify exposures and may influence dose-response relationships for cumulative risk applications.

The impact of this task will be to expand NCEA’s and the Agency’s knowledge base regarding the application of multimedia, multiple stressor exposure data in cumulative risk assessment.

Examples of research questions to be explored through this task include:

Integration of Cumulative Exposure Assessment Measures within Human Health and Ecological Effects Studies:

- How do scientists rectify differences in exposure measurement error among multiple stressors in cumulative risk studies of different focus (i.e., epidemiology, ecology)? How do the following issues influence exposure measurement error for different stressors and media: differences in spatial and temporal variability of the concentration profile; differences among media in delivering stressors to the receptors with respect to



transport, chemistry, and fate; and differences among sampling methodologies for each specific medium-stressor combinations?

- How can results be compared across epidemiologic studies of health or ecological effects related to exposure to stressors for different exposure scenarios? If results can be compared across epidemiologic studies, can toxicology studies be designed in a complementary manner to address research questions about common exposures/mixtures of exposures to inform multiple events along an adverse outcome pathway? If so, how can exposures be generated for toxicology studies to best represent exposures to stressors in epidemiology studies? How does chemical stability of multiple stressors influence such differences?

Integrating Evidence of Human Health and Ecological Effects of Pollution Exposure among Different Media:

- How can risk be apportioned for specific exposures to or sources of multiple stressors when the EPA regulates pollution by medium?
- How (or to what degree) can risk be quantified for non-chemical stressors and other factors not regulated by EPA?
- How should risk be apportioned among different media (e.g., when based on biomonitoring data integrated across multiple sources and routes of exposure)?
- What is the best way for information on different routes of exposure (e.g., inhalation, ingestion, dermal), including information on uncertainties in different media and routes, to be integrated?

Factors Influencing Exposure or Leading to Modification of Health Effects:

- How do diet and behavioral factors influence multiple stressor, multimedia exposures? How do such factors modify effects associated with exposures to stressors via multiple media?
- What behavioral, social, demographic, economic, and other external factors influence multiple stressor, multimedia exposures and modify health effects? Similarly, what factors influence multiple stressor, multimedia exposures and modify ecological effects?

Research Approach:

Researchers will engage in ongoing analyses of multiple stressor and/or multimedia exposures that influence cumulative risk assessment. The results of these analyses will be presented in the peer-reviewed literature, so that they are available for reference in NCEA assessments. Two distinct subtasks focus on advancing NCEA's multiple stressor, multimedia knowledge base through model development and application. Details on products from each are described in the next section.



- **Subtask 6.4.1 (RMS ID# HHRA 3.234.1) : Advances in modeling for exposure apportionment in the study of multiple stressor exposure via multiple media:** This subtask expands NCEA's and the Agency's ability to model multiple stressors by developing and testing three approaches: multiple pathway exposure modeling (using phthalates as a test case), apportionment of exposure via multiple pathway modeling, and apportionment of exposure and risk via modeling of multiple stressors' physical and chemical properties.

(RMS ID# HHRA 3.234.1.1) Modeling dermal and inhalation exposures to diethyl- and di(1 n-butyl) phthalate: The EPA will investigate the two main pathways for phthalate exposure (consumer products and diet), focusing on two phthalates with the potential to extrapolate the results to other phthalates. The objective of this work is to model the full pathway of air-skin/lung-bladder to predict urine concentrations for comparison with experimentally measured concentrations of DEP and DnBP metabolites. While the experimental data provides a "proof of concept" for the importance and differences in dermal and inhalation intakes, the modeling provides a predictive tool that can then be extrapolated to the general population, occupational, or other settings to characterize the exposures resulting from air concentrations of DnBP and DEP.

(RMS ID# HHRA 3.234.1.2) Apportioning chemical stressors for the most affected portions of exposed populations of humans and ecological receptors: This study will review the published studies of cumulative exposures to mixtures and investigate how new research can be applied to the task of apportionment for specific populations. The project will also analyze the predictions of cumulative exposures that will be generated by several modeling approaches. The work would seek to determine when the upper bound of a population is driven by one or two stressors and when groups of stressors drive risk and to develop ways of identifying the specific drivers of the impacts in the upper bound.

(RMS ID# HHRA 3.234.1.3) Chemical and physical properties of multiple stressors and cardiovascular effects: NCEA exposure assessment scientists have been participating in a collaboration with scientists from academia to study the impact of multiple stressors on cardiovascular disease (CVD) risk factors. The study will continue this work by identifying the physicochemical properties of a wider set of air pollutants contributing to CVD risk factors using quantitative structure activity relationship (QSAR) models and estimate epidemiologic associations between CVD risk factors and multiple stressors



using an epidemiologic model that includes the physicochemical properties of pollutants identified by the QSAR models.

- **Subtask 6.4.2 (RMS ID# HHRA 3.234.2): Application of exposure apportionment in the study of multiple stressor exposure via multiple media:** The methodologies developed above will be applied to investigate how exposures can be apportioned for two specific cases. First, pathway analysis will be applied to study breast milk as a route of exposure for multiple stressors and nutrients. Second, exposures to multiple stressors will be apportioned for multiple media in a test city (Philadelphia) for which the Agency holds a substantial amount of data.

(RMS ID# 3.234.2.1) Breastfeeding as a route of exposure for environmental chemicals: The purpose of this study is to provide a comprehensive literature evaluation on the potential for negative health consequence to infants from exposure to chemicals in breast milk. The core goal of the health outcome evaluation will be a comprehensive assessment and quality review of the epidemiological literature where mother-infant cohorts have been tracked over time to assess health impacts and biomarker changes.

(RMS ID# 3.234.2.2) Cumulative exposures, social determinants, and health in Philadelphia: This study will combine ambient concentration data for criteria air pollutants and benzene with survey data on health, fast food consumption, sugary beverage consumption, tobacco usage, number of servings of fruits and vegetables, sodium intake, access and quality to fresh produce, and availability of green space to analyze associations between ambient pollutants and other determinants of health.

(RMS ID# 3.234.2.3) Simple pharmacokinetic modeling of infant body burden impacts from exposure to persistent bioaccumulative compounds in mother's milk: This work continues the evaluation of infant impacts from chemicals in mother's milk in an exposure study with the use of simple pharmacokinetic (PK) models. Infant body burden data from pooled blood samples has been obtained by Australian researchers on chemicals important to IRIS and EPA program offices including PCB and PBDE congeners, and DDE, at half-year increments from birth till the age of 4. A simple PK model is parameterized and tested against this data, to show how infant body burdens are elevated in the months to early years following birth, compared to impacts from much less chemical exposure through infant formula.

(RMS ID# HHRA 3.234.2.4) Residential exposure to pesticide active ingredients and birth defects: This work examines the association of exposure to common active



ingredients found in pesticides and risk of 10 birth defect phenotypes for which previous associations with pesticides have been reported. Pesticide exposure is assigned using a previously constructed metric estimating pounds of active ingredient applied to crops within 500 meters of maternal residence, specific dates of pregnancy, and chemical application dates based on the planting/harvesting dates of each crop. Birth defect cases are identified from the North Carolina Birth Defects Monitoring Program and linked to live singleton birth records for 2003-2005 in North Carolina; non-cases serve as controls.

Task Products:

- **Subtask 6.4.1 (RMS ID# HHRA 3.234.1): Advances in modeling for exposure apportionment in the study of multiple stressor exposure via multiple media**
 - **Product 6.4.1.1. (RMS ID# HHRA 3.234.1.1)**
 - **Product Title: Modeling of dermal and inhalation exposures to diethyl- and di(1 n-butyl) phthalate**
 - Product Contact (email): [[HYPERLINK "mailto:lorber.matthew@epa.gov"](mailto:lorber.matthew@epa.gov)]
 - Product's Delivery Date: September 30, 2017
 - Product Description: One peer-reviewed journal article submission
 - Product's Contribution to Output: This manuscript will inform cumulative risk assessment efforts related to consideration of phthalate exposure mixtures.
 - Product's Timeline (with milestones): Draft of manuscript for internal clearance anticipated 1st Quarter FY17
 - Product's intended user/customer/audience: IRIS and Program Office (particularly OPPT) who are conducting assessments on phthalates.
 - Is this a key product? No
 - Does this Product contribute to a Product under another Task? Yes. This project will be useful to IRIS assessments on phthalates and of interest to OCSPP.
- **Product 6.4.1.2. (RMS ID# HHRA 3.234.1.2)**
- **Product Title: Apportioning chemical stressors for the most affected portions of exposed human populations and ecological receptors**
- Product Contact (email): [[HYPERLINK "mailto:price.pauls@epa.gov"](mailto:price.pauls@epa.gov)]
- Product's Delivery Date: September 30, 2017, December 30, 2018
- Product Description: Two peer-reviewed journal article submissions
- Product's Contribution to Output: Two manuscripts are being planned for this sub-task. Both manuscripts will inform cumulative risk assessment efforts in the apportionment of chemicals in exposed populations of humans and ecological receptors. The first will include an analysis of phthalate data from the National Health and Nutrition Examination Survey (NHANES), and the second will entail a simulation study.



- Product's Timeline (with milestones): Draft of first manuscript for internal clearance anticipated 2nd quarter of FY17. Draft of second manuscript for internal clearance anticipated 3rd quarter of FY18. Product's intended user/customer/audience: Program Offices (particularly OPPT). This work will also support other projects in the HHRA program, as well as the CSS and SHC research programs.
- Is this a key product? Yes (first manuscript only).
- Does this Product contribute to a Product under another Task. Yes. These products will support work in Subtasks 6.1 and 6.2.

- **Product 6.4.1.3. (RMS ID# HHRA 3.234.1.3)**
- **Product Title: Chemical and physical properties of multiple pollutants and cardiovascular effects**
- Product Contact (email): [HYPERLINK "mailto:richmond-bryant.jennifer@epa.gov"]
- Product's Delivery Date: September 30, 2019
- Product Description: One peer-reviewed journal article submission
- Product's Contribution to Output: This manuscript will be available for citation in government reports on cumulative risk assessment and in the Integrated Science Assessments.
- Product's Timeline (with milestones): Draft of manuscript for internal clearance anticipated 1st Quarter FY19
- Product's intended user/customer/audience: NCEA and OAQPS
- Is this a key product? No
- Does this Product contribute to a Product under another Task? Yes. This contributes to Tasks under Project 2, Integrated Science Assessments.

- **Subtask 6.4.2 (RMS ID# HHRA 3.234.2): Application of exposure apportionment in the study of multiple stressor exposure via multiple media**

- **Product 6.4.2.1. (RMS ID# HHRA 3.234.2.1)**
- **Product Title: Breastfeeding as a route of exposure for environmental chemicals**
- Product Contact (email): [HYPERLINK "mailto:lorber.matthew@epa.gov"]
- Product's Delivery Date: September 30, 2017
- Product Description: One peer-reviewed journal article submission
- Product's Contribution to Output: This manuscript will be available for citation in government reports on cumulative risk assessment and in the Integrated Science Assessments.
- Product's Timeline (with milestones): Draft of manuscript for internal clearance anticipated 4th Quarter FY16
- Product's intended user/customer/audience: NCEA, Office of Children's Health Protection (OCHP)



- Is this a key product? No.
- Does this Product contribute to a Product under another Task? This product will likely inform exposure considerations for CRA case studies in Task 6.2 (*RMS ID# HHRA 2.232*).

- **Product 6.4.2.2. (*RMS ID# HHRA 3.234.2.2*)**
- **Product Title: Cumulative exposures, social determinants, and health in Philadelphia**
- Product Contact (email): [[HYPERLINK "mailto:richmond-bryant.jennifer@epa.gov"](mailto:richmond-bryant.jennifer@epa.gov)]
- Product's Delivery Date: September 30, 2019
- Product Description: One peer-reviewed journal article submission
- Product's Contribution to Output: This manuscript will inform urban cumulative risk assessment efforts in the apportionment of chemicals for human exposure.
- Product's Timeline (with milestones): Draft of manuscript for internal clearance anticipated 2nd quarter of FY19
- Product's intended user/customer/audience: Program Offices (particularly OPPT). This work will also support work across the HHRA program as well as the CSS, and SHC research programs. It is also of keen interest to Region 3.
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? Yes. This product will help to inform case studies in Task 6.2.

- **Product 6.4.2.3. (*RMS ID# HHRA 3.234.2.3*)**
- **Product Title: Simple pharmacokinetic modeling of infant body burden impacts from exposure to persistent bioaccumulative compounds in mother's milk**
- Product Contact (email): lorber.matthew@epa.gov
- Product's Delivery Date: September 30, 2017
- Product Description: One peer-reviewed journal article submission
- Product's Contribution to Output: This peer-reviewed manuscript will inform cumulative risk assessment efforts related to infant impacts from exposure to multiple chemicals.
- Product's Timeline (with milestones): Draft of manuscript for internal clearance anticipated 2nd quarter of FY17
- Product's intended user/customer/audience: Program Offices (particularly OCHP and OPPT). This work will also support work across the HHRA program as well as the CSS research programs.
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? Yes. This product will help to inform case studies in Task 6.4.2.1

- **Product 6.4.2.4. (*RMS ID# HHRA 3.234.2.4*)**
- **Product Title: Residential exposure to pesticide active ingredients and birth defects**
- Product Contact (email): [[HYPERLINK "mailto:luben.tom@epa.gov"](mailto:luben.tom@epa.gov) \t "_blank"]



- Product's Delivery Date: September 30, 2017
- Product Description: One peer-reviewed journal article submission
- Product's Contribution to Output: This peer-reviewed manuscript will inform cumulative risk assessment efforts related to reproductive and developmental impacts from exposure to multiple chemicals.
- Product's Timeline (with milestones): Draft of manuscript for internal clearance anticipated 3rd quarter of FY17
- Product's intended user/customer/audience: Program Offices (particularly OPP). This work will also support work across the HHRA program as well as the CSS, and SHC research programs.
- Is this a key product? No.
- Does this Product contribute to a Product under another Task? No.

References:

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De Brouwere K, Cornelis C, Arvanitis A, Brown T, Crump D, Harrison P, Jantunen M, Price P, Torfs R. (2014). Application of the maximum cumulative ratio (MCR) as a screening tool for the evaluation of mixtures in residential indoor air. *Science of the Total Environment* 479–480 (2014) 267–276

Gong M, Zhang Y, Weschler CJ. Predicting dermal absorption of gas-phase chemicals: transient model development, evaluation, and application. *Indoor Air* 2014; 24: 292-306.

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Meng Q, Richmond-Bryant J, Davis JA, Cohen J, Svendsgaard D, Brown JS, Tuttle L, Hubbard H, Rice J, Kirrane E, Vinikoor-Imler L, Kotchmar D, Hines E, Ross M. Sensitivity of blood lead-air lead slope factors to particle size distribution of ambient air lead. *Environmental Science and Technology*. 2014; 48:1263-1270.

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Task Constraints:

For all of the research activities in the seven subtasks, inferences from the study results are constrained by the quality and availability of exposure and health data used in the studies. Execution of each of the sub-tasks is also constrained by the availability of funding and FTEs for EPA staff and extramural resources for contracted researchers.

Task Dependencies:

Successful implementation of the research described in Sub-tasks 6.4.1-6.4.2 is contingent upon availability of data and of staff time to complete the studies. It is also dependent on availability of extramural resources for a contracted post-doctoral researcher. Release of any published reports for either government or peer-reviewed publications depends on efficient and timely internal review and clearance processes.

Task Quality Assurance and Data Management Needs:



- Is there an existing IRP/ QAPP(s) that applies to this Task? If so, identify IRP/QAPP. If new IRP/QAPPs are required, provide the status.
 - Yes. NCEA-16-00004. Quality Assurance Project Plan (QAPP) For HHRA Projects 6, 7, & 8 To Develop Methods, Tools, Models and Supporting Analysis
- Will this Task involve large amounts of data that need a data management plan? If yes, explain.
 - TBD. The Health and Environmental Research Online (HERO) system is used for systematic literature review and is covered by a separate QAPP: NCEA-16-00005. Quality Assurance Project Plan (QAPP) for Extraction of Scientific Data into the Health and Environmental Research Online (HERO) Database System

**Task Resources:**

The following table summarizes resource needs for Task 6.4, including intramural funding dedicated for staff scientists' salaries; extramural funds for contracted scientific support through ORISE, ASPPH, and other contract vehicles; and extramural funds for page charges. The distribution of resources is described on subsequent pages.

Product	Scientist	Div	Priority	Extramural Resources \$				Intramural Resources \$ <i>Includes Only Staff Scientist Salaries</i>			
				FY16	FY17	FY18	FY19	FY16	FY17	FY18	FY19
Task Lead	Jennifer Richmond-Bryant	NCEA-RTP	NA	\$ -	\$ -	\$ -	\$ -	\$ -	\$ -	\$ -	\$ -
6.4.1.1 Modeling of dermal and inhalation exposures to diethyl- and di(1 n-butyl) phthalate	Matthew Lorber	NCEA-W	Low	\$ -	\$2	\$ -	\$ -	\$ -	\$ -	\$ -	\$ -
6.4.1.2-1 Apportioning chemical stressors for the most affected portions of exposed populations of humans and ecological receptors	Paul Price**	NERL	High	*\$15	*\$75.6	*\$47.6	\$ -	\$ -	\$ -	\$ -	\$ -
6.4.1.3 Chemical and physical properties of multiple pollutants and cardiovascular effects	Jennifer Richmond-Bryant	NCEA-RTP	Med	\$ -	\$ -	\$ -	\$2	\$ -	\$ -	\$ -	\$ -
6.4.2.1 Breastfeeding as a route of exposure for environmental chemicals as well as nutrients	Matthew Lorber	NCEA-W	High	*\$46.0	\$ -	\$ -	\$ -	\$ -	\$ -	\$ -	\$ -
6.4.2.2 Cumulative Exposures, Social Determinants, and Health in Philadelphia	Jennifer Richmond-Bryant	NCEA-RTP	Med	\$ -	*\$25.1	*\$47.6	*\$82.7	\$ -	\$ -	\$ -	\$ -
6.4.2.3 Simple pharmacokinetic modeling of infant body burden impacts from exposure to persistent bioaccumulative compounds in mother's milk	Matthew Lorber	NCEA-W	Med	\$ 3.0	\$ -	\$ -	\$ -	\$ -	\$ -	\$ -	\$ -
6.4.2.4 Residential exposure to pesticide active ingredients and birth defects	Tom Luben	NCEA-RTP	Med	\$ -	\$2.5	\$ -	\$ -	\$ -	\$ -	\$ -	\$ -



HHRA Project 6 Plan

TOTAL	\$64.0	\$105.3	\$95.3	\$84.7	\$ -	\$ -	\$ -	\$ -
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*includes \$24K funding for 30% ASPPH fellow (paid by HHRA) and a \$20K no-cost contract extension of obligated FY15/16 funds plus page charges

*includes funding for ORISE post-doc

** FTE paid by NERL.

†includes \$10K for data access subscription



Task Level Extramural Resources

Lab or Center receiving money: NCEA

Division: NCEA-RTP and NCEA-W

Contact name: Jennifer Richmond-Bryant

Total extramural (NPD RAP) in \$K

- FY16: \$64.0
- FY17: \$105.3
- FY18: \$95.3
- FY19: \$84.7

Description of Extramural needs for each FY:

Page charges (\$K):

- FY16: \$2.0
- FY17: \$7.5
- FY18: \$0
- FY19: \$4.0

Contract support (\$K):

- FY16: \$20.0 (no-cost extension of funds obligated for FY15/16)
- FY17: \$10 (data subscription)
- FY18: \$0
- FY19: \$0

Fellowship support (\$K, mechanism):

- FY16: \$49.0 (\$24K for ASPPH fellow; \$15K for ORISE fellow)
- FY17: \$90.8
- FY18: \$95.3
- FY19: \$82.7

Description of impact on product delivery (or contribution) if resources are not available in a timely manner?

Without adequate resources, the proposed products will not be completed.



Proposed method for extramural fellowship support

Product	Funding Source	Funding Amount (\$K)	New or Existing
6.4.1.2 Apportioning chemical stressors for the most affected portions of exposed populations of humans and ecological receptors	ORISE postdoc (FY16-18)	FY16: \$15.0 FY17: \$75.6 FY18: \$47.6	New
6.4.2.1 Breastfeeding as a route of exposure for environmental chemicals as well as nutrients	ASPPH Fellow (FY16)	\$24.0 (30% of full-time)	Existing
6.4.2.2 Cumulative exposures, social determinants, and health in Philadelphia	ORISE postdoc (FY17-19)	FY17: \$15.1 FY18: \$47.6 FY19: \$82.7	New



Task Level Intramural Resources

Intramural (L/C Corporate) in \$K

- FY16: \$0
- FY17: \$0
- FY18: \$0
- FY19: \$0

Description of Intramural Needs for each FY:

The only intramural needs are FTE, as detailed below.

Special Task Level Resource Needs and Considerations

Special facilities or equipment needed: NA

Identify any of the following that apply:

- High performance computing/visualization: NA
- Regional Applied Research Effort (RARE): NA
- Regional Methods (RM): NA
- Pathfinder Innovation Project (PIP): NA
- Tech transfer/CRADAs: NA
- Requires Significant Travel (i.e., field studies, site visits, etc.): NA

Task Staffing

Staff Member	L/C	Division	Expertise	Contribution to Task or Product	FY16 %FTE	FY17 %FTE	FY18 %FTE	FY19 %FTE
Jennifer Richmond-Bryant	NCEA	RTP	Exposure assessment	Task lead	5	5	5	5
				6.4.1.3 Chemical and Physical Properties	5	10	10	5
				6.4.2.2 Cumulative exposures, social determinants, and health in Philadelphia	5	10	10	10
Matthew Lorber	NCEA	DC	Cumulative risk assessment	6.4.1.1 Phthalate cumulative risk research	10	5	0	0
				6.4.2.1 Chemicals in Breast Milk	10	10	0	0
				6.4.2.3 Simple pharmacokinetic modeling of infant body burden impacts from exposure to persistent bioaccumulative compounds in mother's milk	10	10	0	0
Paul Price	NERL	RTP	Computational exposure assessment	6.4.1.2 Apportioning chemical stressors for the most affected portions of exposed populations	20	10	10	0
Tom Luben	NCEA	RTP	Epidemiology	6.4.2.4 Residential exposure to pesticide active ingredients and birth defects	0	2	0	0
Kristen Rappazzo (collaborator)	NHEERL	RTP	Epidemiology	6.4.2.4 Residential exposure to pesticide active ingredients and birth defects	0	0	0	0

Percent FTE reflects Sub-tasks 6.4.1.1-6.4.2.2 detailed above. If additionally identified research gaps necessitate new research Sub-tasks, 5-10% FTE would be anticipated to be needed per year per individual to implement each Sub-task.